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Treatment of Refractory *Mycobacterium avium* Complex Lung Disease with a Moxifloxacin-Containing Regimen

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Moxifloxacin (MXF) has *in vitro* and *in vivo* activity against *Mycobacterium avium* complex (MAC) in experimental models. However, no data are available concerning its treatment effect in patients with MAC lung disease. The aim of this study was to evaluate the clinical efficacy of an MXF-containing regimen for the treatment of refractory MAC lung disease. Patients with MAC lung disease who were diagnosed between January 2002 and December 2011 were identified from our hospital database. We identified 41 patients who received MXF for ≥4 weeks for the treatment of refractory MAC lung disease. A total of 41 patients were treated with an MXF-containing regimen because of a persistent positive culture after at least 6 months of clarithromycin-based standardized antibiotic therapy. The median duration of antibiotic therapy before MXF administration was 410 days (interquartile range [IQR], 324 to 683 days). All patients had culture-positive sputum when MXF treatment was initiated. The median duration of MXF administration was 332 days (IQR, 146 to 547 days). The overall treatment success rate was 29% (12/41), and the median time to sputum conversion was 91 days (IQR, 45 to 190 days). A positive sputum acid-fast-bacillus smear at the start of treatment with MXF-containing regimens was an independent predictor of an unfavorable microbiological response. Our results indicate that MXF may improve treatment outcomes in about one-third of patients with persistently culture-positive MAC lung disease who fail to respond to clarithromycin-based standardized antibiotic treatment. Prospective studies are required to assess the clinical efficacy of MXF treatment for refractory MAC lung disease.

Pulmonary disease caused by nontuberculous mycobacteria (NTM) appears to be increasing worldwide (1–6). *Mycobacterium avium* complex (MAC), consisting of *Mycobacterium avium* and *Mycobacterium intracellulare*, is the most common etiologic agent in lung disease caused by NTM (1, 2). A major therapeutic advance in the treatment of MAC lung disease was the introduction of newer macrolides such as clarithromycin (CLR) and azithromycin, which have *in vitro* and clinical activity against MAC disease (1, 2). Macrolides, together with ethambutol (EMB) and rifampin (RIF), are the cornerstones of MAC therapy (1, 2). However, the treatment success rate for MAC lung disease is unsatisfactory. Macrolide-based therapy results in the successful eradication of an MAC pulmonary infection in only 60 to 80% of cases (7–10). Many patients fail to respond to treatment, relapse, or develop CLR-resistant MAC disease after receiving macrolide-based therapy (7–10).

Moxifloxacin (MXF) is an 8-methoxy fluoroquinolone with better *in vitro* activity than older quinolones against MAC (11). Murine experimental infection models showed that MXF exhibited favorable activities against MAC *in vitro* and *in vivo* (12, 13). Although MXF is not formally recommended for the treatment of MAC lung disease, it has been frequently prescribed in routine clinical practice, partly as a result of the unsatisfactory rate of response to recommended first-line regimens (14). However, no data are available concerning its effect on MAC lung disease. The aim of this study was to evaluate the clinical efficacy of an MXF-containing regimen for the treatment of MAC lung disease.

MATERIALS AND METHODS

Patients. Consecutive patients with MAC lung disease who were diagnosed between January 2002 and December 2011 were identified from the NTM Registry of Samsung Medical Center (a 1,961-bed referral hospital in Seoul, South Korea) (10, 15, 16). During this 10-year period, 913 patients were diagnosed with MAC lung disease. All of the patients met the diagnostic criteria for NTM lung disease according to American Thoracic Society guidelines (1). Of these patients, 494 (54%) began long-term antibiotic treatment on 31 December 2011. Ultimately, we identified patients who received MXF for ≥4 weeks for the treatment of refractory MAC lung disease. The Institutional Review Board at our institution approved this retrospective study; informed consent for the use of patient medical data was waived.

Antibiotic treatment. All of the patients with MAC lung disease who began antibiotic therapy received standardized combination oral antibiotic therapy (1). For most patients, the regimen included CLR at 1,000 mg/day, EMB at 15 mg/kg/day, and RIF at 450 mg/day (body weight < 50 kg) or 600 mg/day (body weight ≥ 50 kg). Streptomycin was administered intramuscularly in 13 (32%) patients with severe fibrocavitary disease or CLR-resistant MAC lung disease before MXF treatment.

The indication of MXF-containing antibiotic treatment for refractory MAC lung disease in this study was a persistent positive culture after at least 6 months of CLR-based standardized antibiotic therapy. All patients had culture-positive sputum when MXF treatment was initiated. A daily dose of 400 mg of MXF was prescribed. Sputum conversion was defined as three consecutive negative cultures; the time of conversion was defined as the date of the first negative culture. Treatment success was defined as negative cultures for the infecting MAC strains for 12 months or longer

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TABLE 1 Baseline characteristics of 41 patients with *Mycobacterium avium* complex lung disease who were treated with a moxifloxacin-containing antibiotic regimen

Patient characteristic[a]	Values[b]
Age, yr	65 (56–71)
Male	28 (68)
Body mass index, kg/m^2	19.5 (18.2–21.2)
Current or ex-smoker	19 (46)
History of previous tuberculosis	29 (71)
Pulmonary function test	
FEV_1	84% (65–94%)
FVC	75% (63–90%)
FEV_1/FVC	80% (69–89%)
Etiologic organism	
Mycobacterium avium	15 (37)
Mycobacterium intracellulare	26 (63)
Positive sputum AFB smear[c]	29 (71)
No. of involved lobes	4 (3–4)
Type of disease	
Fibrocavitary form	19 (46)
Nodular bronchiectatic form	20 (49)
Unclassifiable form	2 (5)

[a] FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; AFB, acid-fast bacillus.
[b] Data represent number (percent) or median (interquartile [IQR] range) except where otherwise indicated.
[c] Data represent patient status at the time of start of moxifloxacin treatment.

TABLE 2 MIC breakpoints and *in vitro* susceptibility of *Mycobacterium avium* complex ($n = 40$)

Drug[a]	Drug concn (μg/ml)	No. of strains distributed at the MIC (μg/ml)[b]										
		0.125	0.25	0.5	1	2	4	8	16	32	64	>64
CLR ($n = 40$)	0.5–64			**17**[c]	**9**	**4**	**3**				*2*	*5*
MXF ($n = 40$)	0.125–16		**2**	**6**	**7**	14	*8*	*3*				
EMB ($n = 22$)	0.25–32						*4*	*3*		*15*[d]		
RIF ($n = 36$)	0.125–16		**1**	**1**		4	6	*9*	*15*[d]			

[a] CLR, clarithromycin; EMB, ethambutol; RIF, rifampin; MXF, moxifloxacin.
[b] Boldface roman and lightface italic characters indicate susceptible and resistant categories of interpretive criteria to each antimicrobial agent, respectively.
[c] Low offscale MICs were converted to the next-lowest concentration.
[d] High offscale MICs were converted to the next-highest concentration.

after the initiation of MXF therapy (17). We excluded two patients who received an adjunctive surgery with less than 2 months of MXF therapy, because the treatment effect of MXF could not be evaluated.

Drug susceptibility tests. Drug susceptibility testing was performed at the Korean Institute of Tuberculosis. The MICs of CLR, RIF, EMB, and MXF were determined using the broth microdilution method as described by the Clinical and Laboratory Standards Institute (CLSI) (18). The drug concentration ranges for tested drugs were as follows: for CLR, 0.5 to 64 μg/ml; for MXF, 0.125 to 16 μg/ml; for EMB, 0.25 to 32 μg/ml; and for RIF, 0.125 to 16 μg/ml. MAC isolates with an MIC ≤ 8 μg/ml were regarded as susceptible to CLR, while those with an MIC ≥ 32 μg/ml were regarded as resistant. An isolate with an MIC ≤ 1 μg/ml was defined as susceptible to MXF, while that with an MIC ≥ 4 μg/ml was defined as resistant (18). Breakpoints for the susceptibility and resistance of MAC to RIF and EMB have not been defined by the CLSI. In this study, isolates were considered resistant if the RIF or EMB MIC was ≥8 μg/ml (19).

Statistical analysis. All data are presented as medians and interquartile ranges (IQR) for continuous variables and as numbers (percentages) for categorical variables. Categorical variables were analyzed using Pearson's χ^2 test or Fisher's exact test. Multivariable logistic regression analysis was performed to assess the effects of independent factors on the final treatment outcome. Variables with a P value ≤ 0.2 by univariable analysis were considered for multivariable analysis (20). All P values were two sided, with $P < 0.05$ considered to be statistically significant. All of the statistical analyses were performed using PASW 18.0 (SPSS Inc., Chicago, IL); a two-sided $P < 0.05$ was considered significant.

RESULTS

Clinical characteristics of the patients. A total of 41 patients (28 males and 13 females; median age, 65 years [IQR, 56 to 71 years]) with MAC lung disease who were treated using an MXF-containing regimen were included in the study. The median body mass index was 19.5 kg/m^2 (IQR, 18.2 to 21.2 kg/m^2). None of the patients were positive for HIV infection. The baseline characteristics of the patients are summarized in Table 1.

The etiologic agents included *M. avium* in 15 patients (37%) and *M. intracellulare* in 26 patients (63%). A total of 29 patients (71%) had a positive acid-fast-bacillus (AFB) smear at the time of MXF treatment initiation. A total of 19 patients (46%) had the fibrocavitary form of MAC lung disease, 20 patients (49%) had the nodular bronchiectatic form, and 2 patients (5%) had an unclassifiable form.

Drug susceptibility test results were available for 40 patients (98%). The MAC isolates recovered from seven patients (18%) showed resistance to CLR, while 11 isolates (28%) were resistant to MXF (Table 2).

MXF-containing antibiotic treatment. All patients were treated with an MXF-containing regimen because of a persistent positive culture after at least 6 months of CLR-based standardized antibiotic therapy. The median duration of CLR-based antibiotic therapy before MXF administration was 410 days (IQR, 324 to 683 days). Streptomycin was continuously administered in eight patients and newly administered in five patients with the MXF-containing regimen; the median duration of streptomycin use was 159 days (IQR, 78 to 248 days) in these patients.

The duration of MXF administration was a median of 332 days (IQR, 146 to 547 days) in 41 patients. However, MXF was discontinued during antibiotic therapy in 33 patients. The reasons for discontinuation were a persistent positive culture despite the administration of MXF ($n = 21$; median, 413 days; IQR, 172 to 682 days), adverse effects associated with MXF such as a gastrointestinal disturbance or skin rash ($n = 10$; median, 62 days; IQR, 36 to 237 days), death related to MAC lung disease ($n = 2$; medians, 106 and 156 days), and other ($n = 1$; median, 98 days).

Treatment outcomes. Of 41 patients with MAC lung disease with persistent positive cultures after at least 6 months of CLR-based antibiotic therapy, 12 became sputum negative after MXF therapy. The median time to sputum conversion was 91 days (IQR, 45 to 190 days). Among these 12 patients with treatment success, eight patients received MXF to the end of antibiotic treatment for a median of 521 days (IQR, 415 to 598 days) and the median time to sputum conversion was 79 days (IQR, 45 to 190 days). Although MXF was discontinued in four patients after a median of 87 days (IQR, 45 to 125 days), sputum culture converted to negative after a median of 91 days (IQR, 49 to 119 days). Therefore, the overall treatment success rate was 29% (12/41) and

TABLE 3 Predictors of treatment failure in patients with *Mycobacterium avium* complex lung disease who were treated with a moxifloxacin-containing antibiotic regimen ($n = 41$)[a]

Patient characteristic	Treatment outcome[b]		Univariable analysis	Multivariable logistic regression	
	Success ($n = 12$)	Failure ($n = 29$)	*P* value	Adjusted OR (95% CI)	*P* value
Male	7 (58)	21 (72)	0.469		
Age > 65 yr	7 (58)	12 (41)	0.493		
Body mass index < 18.5 kg/m^2	3 (25)	11 (38)	0.494		
Current or ex-smoker	6 (50)	13 (45)	0.999		
Previous history of tuberculosis	7 (58)	22 (76)	0.452		
Etiologic organism *Mycobacterium intracellulare*	4 (33)	22 (76)	0.015	4.78 (0.85–26.90)	0.076
Fibrocavitary disease form	5 (42)	14 (48)	0.744		
Positive sputum AFB smear[c]	5 (42)	24 (83)	0.020	6.51 (1.14–37.10)	0.035
Combined use of moxifloxacin and streptomycin	3 (25)	10 (34)	0.719		
Use of rifabutin instead of rifampin	5 (42)	8 (28)	0.469		
Total no. of drugs	4 (4–4)	4 (4–5)	0.796		
In vitro resistance[d]					
Clarithromycin	0/11 (0)	7/29 (24)	0.159	0.21 (0.03–1.26)	0.99
Moxifloxacin	4/11 (36)	7/29 (24)	0.694		

[a] OR, odds ratio; CI, confidence interval; AFB, acid-fast bacillus.
[b] The data are presented as number (percent) or median (interquartile range).
[c] At the start of moxifloxacin treatment.
[d] Data were available for 40 patients.

sputum culture conversion failed in 29 patients (71%). Two patients died of MAC lung disease.

After MXF treatment, follow-up drug susceptibility tests were performed in 18 patients among 29 patients with treatment failure. CLR resistance rates increased from 28% (5/18) to 67% (12/18) and MXF resistance rates also increased from 22% (4/18) to 67% (12/18) in these patients.

Prognostic factors. The treatment success rates did not differ between those patients whose isolates were resistant to MXF (36%, 4/11) and those whose isolates were susceptible or intermediate to MXF (24%, 7/29) ($P = 0.694$).

Based on the clinical variables included in our univariable comparison between the treatment success and treatment failure groups, the final multiple logistic regression model revealed that a positive sputum AFB smear at the start of treatment with MXF-containing regimens was an independent predictor of an unfavorable microbiological response (odds ratio, 6.51; 95% confidence interval, 1.143 to 37.10; $P = 0.035$) (Table 3).

DISCUSSION

Although MXF showed *in vitro* and *in vivo* activity against MAC in experimental models, there are essentially no data demonstrating the treatment effect of fluoroquinolones for MAC lung disease. To our knowledge, this is the first study to evaluate the clinical efficacy of MXF for the treatment of MAC lung disease. This study included 41 patients with persistently culture-positive MAC lung disease who failed to respond to CLR-based standardized antibiotic treatment. According to our results, about one-third of the patients showed a favorable treatment outcome. Although this finding is potentially confounded by the concurrent use of streptomycin or surgical resection, it raises an important clinical question, since it indicates that the addition of MXF might improve the outcomes in patients with refractory MAC lung disease.

For MAC lung disease, the treatment response rate to the standard regimen is unsatisfactory (7–10). Therefore, physicians frequently encounter patients who fail to respond to prior antibiotic therapy. However, the optimal treatment regimen has not been established for these patients. Of the alternative drugs for the treatment of MAC lung disease, fluoroquinolones have been studied the most. In the past, when other fluoroquinolones such as ciprofloxacin were examined in clinical trials for the treatment of disseminated MAC infection, their contribution was minimal (21). Another study of the treatment of MAC lung disease with RIF, EMB, and ciprofloxacin showed outcomes no better than those of studies using just RIF and EMB (22). Later, MXF was shown to have a much more favorable *in vitro* and *in vivo* mouse model profile (11–13, 23). Also, MXF has been shown to achieve very high levels in human alveolar macrophages and lung epithelial lining fluid, which may indicate clinical effectiveness (24). However, concomitant treatment with RIF and MXF could cause a significant decrease of MXF exposure and have an effect on the pharmacokinetic parameters (25).

Existing data regarding the efficacy of MXF for the treatment of MAC infection are controversial. A recent experimental study revealed that mild antagonism occurred between MXF and CLR when they were given in combination, and this seemed to be MAC strain dependent (26). In addition, using a fluoroquinolones as the only companion drugs for CLR in MAC treatment regimens was associated with the development of CLR-resistant MAC strains (17). Thus, further study is required to evaluate the precise roles of MXF in the treatment of MAC lung disease.

In this study, the indication for MXF administration in patients with MAC lung disease was a persistent positive culture after standardized antibiotic therapy, although they received recommended combination antibiotic treatment for a median of 410 days (IQR, 324 to 683 days). Because it was certain that the continuation of previous drug therapy would be unsuccessful, it was encouraging that about one-third of patients showed a favorable treatment outcome after the addition of MXF. Interestingly, the treatment success rate was lower in the CLR-resistant MAC group (0/7, 0%) than in CLR-susceptible MAC group (11/33, 33%), al-

though this is not statistically significant because of a small sample size. These findings suggested that the addition of MXF would be beneficial in patients with MAC lung disease who are unresponsive to initial treatment and remain CLR susceptible.

Revised CLSI guidelines recommend that susceptibility tests for MXF be considered for CLR-resistant MAC isolates and/or isolates from patients who cannot tolerate macrolide therapy, and they propose tentative breakpoints for MXF (18). These newly proposed breakpoints for MXF have not been validated in clinical studies. In our study, 28% of the MAC isolates were resistant to MXF (MIC $\geq$ 4 μg/ml). However, the treatment success rates in patients whose isolates were resistant to MXF were not different from those in patients whose isolates showed susceptibility or intermediate susceptibility to MXF. The clinical usefulness of drug susceptibility testing in the management of patients with MAC lung disease is controversial. Previous studies suggested that there is a strong correlation between the *in vitro* and *in vivo* responses to CLR but no correlation between the *in vitro* MICs for RIF, EMB, and streptomycin and the *in vivo* response in patients with MAC lung disease (27, 28). These observations suggested that the correlation between MIC and clinical response could separate first- and second-tier agents for MAC therapy and that MXF could be at best a second-tier agent. Additional studies are needed to establish the correlation of *in vitro* results with the clinical response to MXF in MAC infection.

In previous studies, MXF (400 mg/day) was well tolerated in patients with multidrug-resistant tuberculosis (MDR-TB) (25, 29, 30). In the present study, however, 10 patients (24%) discontinued MXF due to an adverse reaction such as a gastrointestinal disturbance or skin rash after a median of 62 days (IQR, 36 to 237 days). This is partly because patients with NTM lung disease are usually elderly people with underlying comorbidities, while MDR-TB patients are relatively young (31, 32). Interestingly, a recent study using an *in vitro* pharmacokinetics/pharmacodynamics model of MAC infection suggested that 800 mg/day of MXF might be better than 400 mg/day for patients infected with susceptible isolates (33). The safety of long-term therapy with MXF in this elderly population should be evaluated in future studies.

The present study has several limitations that are inherent in all retrospective studies at a single center. First, the addition of MXF was based on the decision of the attending physician without an established institutional protocol. This could be an important selection bias. Second, the number of cases was too small to detect clinically significant findings regarding predictors of favorable or unfavorable responses. Third, the concurrent use of streptomycin or resectional surgery could have influenced the treatment outcome. Therefore, it may not be possible to generalize our treatment response rates to all patients with MAC lung disease with similar indications.

In conclusion, this report suggests that the addition of MXF can improve the outcomes in about one-third of patients with persistently culture-positive MAC lung disease who fail to respond to CLR-based standardized antibiotic treatment. However, the proportion of CLR- and MXF-resistant MAC strains increased after MXF treatment in the treatment failure group. Prospective studies are required to assess the clinical efficacy of MXF treatment for refractory MAC lung disease.

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