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BRIEF REPORT

Preliminary Evaluation of a Sitafloxacin-Containing Regimen for Relapsed or Refractory Pulmonary *Mycobacterium avium* Complex Disease

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Although sitafloxacin (STFX) is known to have a favorable minimum inhibitory concentration for *Mycobacterium avium*, few studies have evaluated the clinical efficacy of an STFX-containing regimen for pulmonary *M avium* complex (MAC) disease. To evaluate the clinical efficacy of STFX-containing regimens for relapsed or refractory pulmonary MAC disease, we retrospectively reviewed 18 patients with pulmonary MAC disease who received STFX for at least 4 weeks for pulmonary MAC disease between January 2008 and February 2016. Of 18 patients, 10 (55.6%) showed improved radiological characteristics and 8 (44.4%) showed negative sputum cultures at 6 months. Regarding the clinical symptoms, improvements were observed in decreasing order in sputum production (77.8%), cough (72.2%), and malaise (55.6%). Common adverse events included nausea or vomiting (38.9%), followed by loose stool or diarrhea (27.8%) and sleepiness (11.1%). Although this study contained a small number of subjects, we describe a STFX-containing regimen that was effective in achieving sputum culture negative conversions and had an acceptable adverse events profile.

Keywords. fluoroquinolone; *Mycobacterium avium* complex; nontuberculous mycobacteria; salvage therapy; sitafloxacin.

Pulmonary *Mycobacterium avium* complex (MAC) disease is becoming more prevalent worldwide [1]. This disease causes progressive deterioration of lung function and possible chronic respiratory failure. Although physicians have wrestled with this disease for a long time, pulmonary MAC disease is refractory in nature and often difficult to control under clinical conditions. According to the 2007 American Thoracic Society/Infectious Disease Society of America (ATS/IDSA) guideline, the standard treatment regimen for pulmonary MAC disease contains a combination of rifampicin (RFP), ethambutol (EB), and macrolides (clarithromycin [CAM] or azithromycin) [2]. Macrolides are the key drug for treatment of MAC disease, and macrolide-containing therapy can eradicate MAC strains in 50%–60% of cases as an initial therapy [2]. However, it is known that microbiological recurrence is relatively common after successful treatment [3, 4]. Because many of these cases are refractory to standard therapy, current treatment regimens for pulmonary MAC disease remain unsatisfactory in these cases. In recent studies, certain fluoroquinolones have been receiving attention as alternative drugs for the therapy of pulmonary MAC disease. Koh et al [5] reported the advantages of moxifloxacin (MFLX)-containing treatments in refractory pulmonary MAC disease. Fujita et al [6] conducted a randomized control trial comparing gatifloxacin (GFLX)-containing regimens and CAM-containing regimens, and showed the noninferiority of GFLX. Sitafloxacin ([STFX] Gracevit) is a fluoroquinolone oral antibiotic that inhibits deoxyribonucleic acid replication in bacteria. It was released in June 2008 and is currently marketed in Japan and Thailand. Sitafloxacin is known to have similar minimum inhibitory concentration in vitro and in vivo for *M avium* when compared with other commercially available quinolones that show the clinical efficacy for pulmonary MAC disease [7]. However, there is limited experience regarding the use of STFX in the treatment of pulmonary MAC disease [8]. Therefore, we conducted a retrospective study to analyze the clinical efficacy of STFX-containing regimens among several teaching hospitals in Japan.

PATIENTS AND METHODS

Study Design and Participants

This was a multicenter retrospective study conducted among 3 teaching hospitals in Japan: National Hospital Organization Kyoto Medical Center (600 beds, Kyoto), Kyoto University Hospital (1121 beds, Kyoto), and Fukuoka University Hospital (915 beds, Fukuoka). To evaluate the clinical efficacy and side effects of STFX-containing regimens, we retrospectively reviewed 18 patients with pulmonary MAC disease who received STFX for at least 4 weeks for pulmonary MAC disease between January 2008 and February 2016. All patients met the 2007 ATS/IDSA diagnostic criteria and tested negative for human immunodeficiency virus infection. Patients were either refractory for a standard therapy or relapse after a standard therapy.

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We considered standard therapy as receiving a combination of macrolide and RFP- or EB-containing regimen. We defined refractory status as presenting continuous positive sputum culture after at least 1 year of standard therapy. The local institutional review boards approved this retrospective study.

Clinical Evaluation

We evaluated treatment response by the negative conversion of sputum culture, radiographic changes of computed tomography (CT) scan data, and clinical symptoms. The negative conversion of expectorated sputum culture was defined as 3 consecutive negative sputum cultures. If sputum was not expectorated, the sputum was considered to have converted to negative [6]. Radiographic changes of CT scan data and clinical symptoms were evaluated as improved, unchanged, or worse at 3 months and 6 months after STFX-containing treatment was started [6, 9]. All radiographic reports were reviewed by 1 and more board certified radiologists. In accordance with previous reports, we defined radiological classification as 3 forms; nodular bronchiectatic (NB) form, fibrocavitary (FC) form, and NB + FC form [10, 11]. Although we did not evaluate dose ranges, we gave STFX between 50 mg and 100 mg ranges according to previous report [12]. Type, frequency, and severity of adverse events were also recorded during the course of treatment with STFX. Severity of adverse events were evaluated according to Common Terminology Criteria for Adverse Events (CTCAE), version 4.0. We extracted all data from the electronic medical records in participants' institutions.

RESULTS

We reviewed 18 patients from participating hospitals. Characteristics of participants are shown in Table 1. Participants were aged 66.6 ± 7.5 years and predominantly infected with *Mycobacterium intracellulare*. Two patients had coinfection with *Pseudomonas aeruginosa*. Sitafloxacin was used because of relapse in 4 patients and refractory state in 14 patients. All patients had received prior treatment for pulmonary MAC disease; 13 (72.2%) and 5 (27.8%) had received 1 and 2 or more regimens, respectively, before starting the STFX-containing regimen. Clarithromycin, RFP, and EB were frequently used as companion drugs with STFX. Two patients also received streptomycin twice a week. The median duration of STFX administration was 12.1 ± 7.3 months. The starting dose of STFX was 100 mg/day for 17 patients and 50 mg/day for 1 patient. Of the 17 patients receiving 100 mg/day STFX, 2 required reduction to 50 mg/day in the course of therapy. Radiological findings were classified into 3 forms; there were 8 patients with the NB form, 4 with the FC form, and 6 with the NB + FC form.

Treatment responses are shown in Table 2. Of 18 patients, 6 (33.3%) and 8 (44.4%) improved their sputum culture status at 3 months and 6 months after therapy, respectively. Eight patients (44.4%) achieved negative conversion of their sputum culture at 6 months. Regarding the clinical symptoms, improvements were seen in sputum production (77.8%), followed by cough (72.2%) and malaise (55.6%), at 6 months. No clinical symptoms changed to worse during STFX treatment.

Regarding the radiological findings, 6 of 8 patients (75.0%) with the NB form showed improvements in the abnormal shadows. By contrast, only 1 of 4 patients (25.0%) with the FC form improved.

Type, frequency, and severity of adverse events observed in this study are shown in Table 3. Gastrointestinal symptoms were most commonly observed as adverse events; of these, nausea was the most frequent. Two patients required dose reduction of STFX because of nausea and diarrhea, and 2 patients finally discontinued the STFX-containing regimen because of diarrhea and bitterness of the drug. Serious adverse events with grade 3 or more were not observed during STFX administration.

Table 1. Characteristic of Participants With Relapsed or Refractory Pulmonary *Mycobacterium avium* Complex Disease[a]

Characteristics	n = 18
Age, years	66.6 ± 7.5
Gender (female)	15 (83.3)
Body mass index, kg/m^2	18.7 ± 2.8
Infected MAC strain (*Mycobacterium intracellulare*)	11 (61.1)
Coinfected microorganism	
Pseudomonas aeruginosa	2 (11.1)
Duration of MAC disease, years	6.0 ± 5.3
Underlying condition	
COPD	4 (22.2)
Asthma	1 (5.6)
Autoimmune disease	3 (16.3)
Use of corticosteroids	1 (5.6)
Radiographic pattern	
Nodular bronchiectatic form	8 (44.4)
Fibrocavitary form	4 (22.2)
NB + FC form	6 (33.3)
History of previous treatment	
One regimen	13 (72.2)
Two or more regimens	5 (27.8)
Companion drugs with STFX	
Clarithromycin	17 (94.4)
Ethambutol	8 (44.4)
Rifampicin	12 (66.7)
Streptomycin	2 (11.1)
Prior drugs used in treatment	
Clarithromycin	18 (100)
Ethambutol	13 (72.2)
Rifampicin	16 (88.9)
Streptomycin	3 (16.7)
Fluoroquinolone (other than STFX)	3 (16.7)

Abbreviations: COPD, chronic obstructive pulmonary disease; FC, fibrocavitary; MAC, *Mycobacterium avium* complex; NB, nodular bronchiectatic; SD, standard deviation; STFX, sitafloxacin.

[a] Data show either number (%) of patients or mean ± SD.

DISCUSSION

Controversy remains regarding the clinical benefits of fluoroquinolone-containing regimens in the treatment of pulmonary

Table 2. Response to Treatment With Sitafloxacin-Containing Regimen[a]

Parameters	3 Months After Therapy			6 Months After Therapy		
	Worse	Unchanged	Improved	Worse	Unchanged	Improved
Clinical symptoms (n = 18)						
Cough	0	8 (44.4)	10 (55.6)	0	5 (27.8)	13 (72.2)
Sputum	1 (5.6)	5 (27.8)	12 (66.7)	0	4 (22.2)	14 (77.8)
Hemosputum	0	13 (72.2)	5 (27.8)	0	12 (66.7)	6 (33.3)
Fever	0	15 (83.3)	3 (16.7)	0	15 (83.3)	3 (16.7)
Malaise	0	13 (72.2)	5 (27.8)	0	8 (44.4)	10 (55.6)
Sputum culture status (n = 18)	1 (5.6)	11 (61.1)	6 (33.3)	0	10 (55.6)	8 (44.4)
Radiological findings (n = 18)						
Nodular bronchiectatic form (n = 8)	0	4 (50.0)	4 (50.0)	0	2 (25.0)	6 (75.0)
Fibrocavitary form (n = 4)	0	2 (50.0)	2 (50.0)	1 (25.0)	2 (50.0)	1 (25.0)
NB + FC form (n = 6)	0	4 (66.7)	2 (33.3)	0	3 (50.0)	3 (50.0)

Abbreviations: FC, fibrocavitary; NB, nodular bronchiectatic.

[a] Data show number (%) of patients.

MAC disease. Although ciprofloxacin-containing regimens failed to show any advantages [13], MFLX-containing regimens showed a certain level of efficacy in the treatment of refractory pulmonary MAC disease [5]. Both STFX and MFLX displayed favorable in vitro and in vivo activities against *M avium* strains [7]; however, STFX exhibited slightly greater therapeutic efficacy than MFLX based on intrapulmonary bacterial elimination [7]. Although the present preliminary study included only a small number of subjects, the results revealed that use of STFX-containing regimens in the treatment of pulmonary MAC disease was clinically effective and acceptable to patients. Eight of 18 patients (44.4%) in our preliminary study achieved negative conversion of sputum culture at 6 months. This therapeutic efficacy compared favorably with MFLX-containing regimens. Radiological findings were improved in 10 of 18 patients (55.6%) at 6 months; however, response to STFX-containing regimens tended to be smaller in patients with the FC than NB form. This observation might be related to the fact that FC disease is known as a factor causing refractory disease with poor prognosis [10, 14]. Fluoroquinolones may cause many adverse events, and long-term use is potentially of concern. Previous studies found that adverse events manifesting as gastrointestinal symptoms were more frequently observed with STFX-containing regimens than MFLX- or GFLX-containing regimens [5, 6]. Our study findings agreed with those results in that gastrointestinal symptoms were the main adverse events that might have hindered prolonged use of fluoroquinolones. However, all but 1 patient could tolerate the gastrointestinal symptoms, and we did not experience serious adverse events such as severe arrhythmia or seizures during STFX administration.

Table 3. Type, Frequency, and Severity of Adverse Events Observed During Sitafloxacin Administration[a]

Type of Adverse Event	Total Number	Grade 1	Grade 2	Grade 3 or More
Nausea	6	5 (83.3)	1 (16.7)	0
Loose stool	3	3 (100)	0	0
Diarrhea	2	1 (50.0)	1 (50.0)	0
Sleepiness	2	1 (50.0)	1 (50.0)	0
Vomiting	1	1 (100)	0	0
Bitterness of drug	1	1 (100)	0	0
ECG changes[b]	1	1 (100)	0	0
Elevation of liver enzymes	1	0	1 (100)	0

Abbreviations: CTCAE, Common Terminology Criteria for Adverse Events; ECG, electrocardiogram.

[a] Data show number (%) of patients. Grade of adverse event was evaluated according to CTCAE, version 4.0.

[b] ECG change of transient QT prolongation was detected in a patient.

This study has several limitations. First, the study had a retrospective design and included only a small number of patients. Although our multicenter study could reduce the recruitment bias, the results should not be overemphasized. Second, because we did not examine the drug susceptibility of STFX or CAM in this study, we could not discuss the relationship between clinical efficacy and drug susceptibility. Furthermore, the assessment tools of clinical efficacy of STFX were not objective. Third, concerns relating to drug resistance with combination therapy are not addressed in this study. Griffith et al [15] warned that combination therapy with CAM and levofloxacin could induce CAM-resistant MAC. Furthermore, because pulmonary MAC patients are known to have possible coinfection with other microorganisms, especially *P aeruginosa* [16], long-term use of fluoroquinolones may induce drug resistance in microorganisms other than MAC. Finally, the follow-up periods of STFX administration in this study were less than those of conventional standard therapy. These shorter follow-up periods might have led to overestimation of the effectiveness of STFX because instances of later recurrence and adverse events of STFX treatment might have been missed. To overcome and clarify these limitations, prospective study is warranted.

CONCLUSIONS

In conclusion, STFX may be effective and acceptable as a salvage therapy for relapsed or refractory pulmonary MAC disease.

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