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Original Article

The Relation Between the Emergence of Fluoroquinolone Resistance and Fluoroquinolone Exposure in New Cases of Active Pulmonary Tuberculosis

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Abstract

OBJECTIVE: This study aimed to determine the ratio of fluoroquinolone (FQ) exposure before the diagnosis of patients with a new case of active pulmonary tuberculosis (TB) and to investigate the correlation of this treatment with the emergence of FQ-resistant strains.

MATERIAL AND METHODS: In this retrospective comparative case series study, a total of 132 patients, who had been diagnosed with adult, culture-positive, active pulmonary TB were reviewed. The FQ group had 30 patients who had had ≥1 time and ≥7 days of FQ exposure within 1 year before the diagnoses. The control group included an equal number of patients with TB with similar demographic characteristics (non-FQ group). Ofloxacin (OFX) and moxifloxacin (MFX) resistance were examined at 2 different concentrations (2 and 4 mg/L for OFX; 0.25 and 0.5 mg/L for MFX).

RESULTS: Of the 132 patients, 30 (22%) had 7 days or longer of FQ monotherapy within 1 year of initiation of anti-TB treatment. FQ resistance was detected in 2 (3.3%) patients. In the FQ group, MFX resistance at 0.25 mg/L concentration was observed in 1 patient, whereas another patient had OFX and MFX resistance at 4 mg/L and 0.5 mg/L concentrations, respectively. In the non-FQ group, no FQ resistance was detected in any of the patients. No statistically significant difference in terms of development of FQ resistance was found between the ratios of FQ and non-FQ groups (p=0.492). Although there was no statistically significant difference, 2 patients, in whom resistance was detected, had FQ exposure before their diagnosis.

CONCLUSION: The FQ exposure ratio before the diagnosis is high (22%) in this cohort that includes patients with new active pulmonary TB, and the presence of patients with FQ resistance (even if only a few) should be a noteworthy and cautionary result in terms of FQ exposure and resistance development.

KEYWORDS: Fluoroquinolones, drug resistance, tuberculosis

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INTRODUCTION

Despite the presence of standard rifampicin (RIF) based first-line regimens and fluoroquinolone (FQ)-based second-line regimens, tuberculosis (TB) and drug-resistant TB are among the most common and fatal infectious diseases around the world [1]. Resistant TB is an ongoing threat in terms of control and elimination [2]. FQs are one of the most important group of anti-tuberculous bactericidal drugs, which are used in the treatment regimens of patients with multidrug resistant (MDR) and extensively drug resistant (XDR) TB [3]. In addition, FQs are one of the most widely prescribed antibiotic classes. Studies indicate that FQs are still the most frequently prescribed antibiotics, even in cases where antibiotics are not required or FQs are not indicated as the first-line treatment, and the reasonable use of the drugs is one of the most addressed subjects [4].

It has been reported that empirical first-line use of FQs for lower respiratory infections and community-acquired pneumonia can mask TB, delay its diagnosis and treatment, and lead to the emergence of FQ-resistant *Mycobacterium tuberculosis* strains because of FQ use before active TB diagnosis. This problem is even more important in regions where TB is endemic [5-12].

This study aimed to determine the frequency of FQ exposure before the diagnosis of patients with a new case of active pulmonary TB and to investigate the relation of this treatment with the emergence of FQ-resistant strains.

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MATERIAL AND METHODS

This single-center retrospective comparative case series study was approved by the local institutional review board (approval #326, dated 17/04/2013) and was carried out in accordance with the principles of the Helsinki Declaration. All the patients meeting the below specified inclusion criteria, who were diagnosed with active pulmonary TB and had their treatment initiated in outpatient clinics and services at the hospital between January 1, 2013, and December 31, 2013, were included.

Inclusion Criteria

a) Greater than 18 years of age
b) Meeting the definition of new case (patients who had no prior TB treatment or who had treatment for less than a month)
c) Positive culture for *M. tuberculosis* complex from sputum and/or bronchial wash and/or lavage

A total of 132 patients met the specified criteria. All of these cases were investigated to determine whether they used FQ ≥1 time and for ≥7 days before the date of positive culture detection. Not only ofloxacin (OFX) and moxifloxacin (MFX) but use of all FQs were considered as exposure. This information was obtained from the medical records, pharmacy, and social security institution. Patients, who were determined to have any FQs prescribed 1 or more times owing to any infectious diagnosis and had used it for ≥7 days, were considered to be as exposed to FQ.

The patients were assigned to the following 2 groups based on the results obtained: FQ group (patients who were determined to have had FQ use history within 1 year before active pulmonary TB diagnosis) and non-FQ group (among the patients who had no FQ use history within 1 year before active pulmonary TB diagnosis, an equal number of patients with demographic characteristics similar to the FQ group).

Sputum samples of both the groups were examined in Löwenstein-Jensen (L-J) medium and liquid-based automated BACTEC 960 (MGIT) system at laboratory of medical microbiology. Susceptibility testing of isolated *M. tuberculosis* complex strains against first-line drugs (i.e., isoniazid [INH], RIF, ethambutol [EMB], and streptomycin [SM]) and second-line FQs (OFX and MFX) were performed per the method described below. Drug resistances were evaluated by a specialist in microbiology in the laboratory and independently from the medical anamnesis of the patients.

MAIN POINTS

- FQ resistance has not been adequately studied in patients with newly active pulmonary TB susceptible to first-line TB drugs.
- It has been reported that the use of FQ before active TB resulted in the emergence of FQ-resistant Mycobacterium tuberculosis strains.
- In cases where TB is considered during the differential diagnosis of lower respiratory tract infections, avoiding FQ monotherapy is important to prevent the selection of FQ-resistant strains.

Antimycobacterial Drug Susceptibility Test

Susceptibility testing against first-line drugs (i.e., INH, RIF, EMB, and SM) and second-line FQs (OFX and MFX) were performed for sputum samples where *M. tuberculosis* complex growth was detected. Antimycobacterial drug susceptibility tests were applied according to the manufacturer's recommendations advised in the guidelines of the Clinical and Laboratory Standards Institute [13]. *M. tuberculosis* H37Rv (ATCC 27294) standard strain was used for quality control. Susceptibility testing of patients' samples against first and second-line drugs (OFX [2 and 4 mg/L], MFX [0.25 and 0.5 mg/L]) were performed using BACTEC 960 (MGIT) system (Becton Dickinson, Sparks, MD, USA).

Statistical Analysis

The Statistical Package for Social Sciences for Windows 15.0 statistics (SPSS Inc.; Chicago, IL, USA) and data analysis software package was used for the statistical analyses of the study. The database was created from non-parametric data, and analyses were performed after data cleansing. The demographic data were analyzed using descriptive statistics, and data were defined on the basis of mean, standard deviation, and minimum and maximum values. The difference between the groups was evaluated with the Fisher's exact test. The limit of significance was considered as $p<0.05$.

RESULTS

In this study, a total of 132 patients meeting the inclusion criteria were scanned, and 30 patients were detected to have used FQ within 1 year before the diagnosis (FQ group). According to this finding, 22% (n=30) of the patients had used FQ. A total of 30 patients who had no FQ use history within 1 year before the diagnosis and with demographic characteristics similar to the study group were selected as the control group (non-FQ group). Of the 60 patients, 13 (21.6%) were women and 47 (78.3%) men. There were 7 female and 23 male patients in the FQ group and 6 female and 24 male patients in the non-FQ group. No statistically significant difference was found in terms of sex distribution between the 2 groups (p=0.756). Overall, the mean age of the 2 groups was 52.8±16.36 (18-79) years. The mean age of the FQ group was 56.8±14.8 years, whereas it was 48.8±17.0 years for the non-FQ group. No statistically significant difference was found in terms of mean age between the 2 groups (p=0.058) (Table 1).

The patients were evaluated for acid-fast bacilli using the smear microscopic examination. A total of 5 patients from the FQ group and 5 from the non-FQ group were diagnosed with smear-negative pulmonary TB. There was no significant difference in terms of smear results between the 2 groups (Table 1). *M. tuberculosis* strains isolated from sputum cultures of all the patients were detected to be susceptible to the first-line anti-tuberculous drugs (i.e., INH, RIF, EMB, and SM).

In this study, 3.3% of all the patients had resistance. In the FQ group, FQ resistance was detected in 2 (6.66%) patients, and these 2 were 61-year-old male patients. In 1 of the 2 patients with FQ resistance, MFX resistance at a concentration of 0.25 mg/L was determined, whereas the other patient had OFX and MFX resistance at 4 mg/L and 0.5 mg/L concentrations, respectively. All other patients were susceptible to FQ.

Table 1. Age, sex and Acid fast bacilli smear distribution of the cases

	Sex*		Age**	AFB smear ***	
	Female n (%)	Male n (%)	Mean±standard deviation (min-max)	AFB (+)	AFB (-)
FQ Group	7 (23.3)	23 (76.6)	56.8 ±14.8 (27-78)	25	5
NonFQ Group	6 (20)	24 (80)	48.8 ±17.0 (18-79)	25	5
Total	13 (21.6)	47 (78.3)	52.8 ±16.36 (18-79)	50	10

AFB: Acid fast bacilli; FQ: Fluoroquinolone
*p=0.756, There was no statistically significant difference in terms of sex between FQ Group and non-FQ Group.
**p=0.058, There was no statistically significant difference in terms of mean age between FQ Group and non-FQ Group; ***There was no difference in terms of smear results between FQ GroupA and non-FQ Group

Table 2. Number of patients resistant/susceptible to ofloxacin and moxifloxacin

		FQ Group (n)	Non-FQ Group (n)
OFX	2 mg/L	0	0
	4 mg/L	1*	0
MFX	0.25 mg/L	1	0
	0.50 mg/L	1*	0
Susceptible		28	30

FQ: Fluoroquinolone; OFX: Ofloxacin; MFX: Moxifloxacin
*In FQ Group, 1 patient was drug-resistant against both ofloxacin (at 4 mg/L concentration) and moxifloxacin (at 0.50 mg/L concentration)

No statistically significant difference was found in terms of FQ resistance development between the ratios of the FQ and non-FQ groups (p=0.492) (Table 2).

When we investigated the FQ exposure before the diagnosis, in the FQ group, the mean duration of FQ use was 13.7±2.21 (7-56) days with 1 patient who had received multiple courses of FQ for a total of 56 days within 1 year before the diagnosis of TB. The patient with resistance against OFX at 4 mg/L concentration and MFX at 0.5 mg/L had used FQ for 14 days. Another patient with resistance against MFX at 0.25 mg/L concentration had used FQ for 7 days.

DISCUSSION

FQs are recommended as the first-line antibiotic by guidelines and widely used for its broad-spectrum properties, established effect of reducing hospital stay, and being cost effective relative to combination therapy [14]. However, it is also known that empirical and wide use of FQs, especially for the treatment of lower respiratory tract infections, masks the TB diagnosis and thus delays the diagnosis and treatment of TB, leading to the spread of the disease and the selection of FQ-resistant strains [15]. The 2 aspects important in the development of FQ resistance in *M. tuberculosis* are the improper use of these drugs in TB regimens and the widespread use against community-acquired pneumonia or other respiratory tract infections and consequent emergence of resistant *M. tuberculosis* strains. In cases where FQs are used as monotherapy or as the sole active drug in unsuccessful combination regimens, the drug becomes ineffective because of the selection of naturally resistant mutants within the medium. Although the minimum time required for the selection of FQ resistance is not clear, a case presentation reported that resistance can develop as early as 13 days in a *M. tuberculosis* strain [5, 11, 16, 17].

FQ resistance is not routinely investigated especially in patients with new cases of active pulmonary TB who are susceptible to first-line TB drugs. We studied the relation between FQ exposure within a 12-month period before the initiation of anti-TB treatment and resistance development in new, culture-positive TB patients. In our region, 22% (30/132) of this cohort was determined to have FQ monotherapy within months before the diagnosis and treatment, which means that FQ monotherapy within 1 year before the diagnosis and treatment was detected in 1 in every 5 patients in this cohort consisting patients with new cases of active pulmonary TB. This high rate of FQ exposure is of particular interest as it highlights the importance of frequency of FQ use and conducting differential diagnosis for TB. Long et al. [18] determined that 17% of the patients diagnosed with pulmonary TB had received FQ monotherapy within the 6-month period before the diagnosis.

In a study conducted in our region, FQ susceptibility was detected in all 47 non-MDR strains [19]. In this study, quinolone resistance was determined in 2 patients with FQ exposure, and (primary) FQ resistance rate was 6.6% in the group with FQ exposure. In our region, resistant strain detection rate is 3.3% in all patients with new cases of active pulmonary TB for which FQ resistance was investigated. Although none of the patients in the group without FQ exposure had FQ resistance, the difference was not statistically significant. Therefore, this study found no statistically significant difference between FQ resistance and FQ exposure. This may be caused by the lack of sufficient number of patients to constitute statistical power. The high cost of the study method prevented the inclusion of more patients. However, 2 patients detected with resistance were in the group that had FQ exposure, which could be interpreted as a noteworthy and cautionary result in terms of the relationship between FQ exposure and resistance development in *M. tuberculosis*.

Migliori et al. [9] reviewed the 24 European guidelines on lower respiratory tract infection/community-acquired pneumonia and reported that the necessity of differential TB diagnosis before the initiation of FQ treatment were not included in some guidelines and that this posed a risk in terms of development of FQ resistance in *M. tuberculosis* and that these guidelines should be updated. In this meta-analysis, FQ exposure before TB diagnosis was detected to cause a 3-fold increase in the risk of resistance development than in the patients without FQ exposure (odds ratio [OR], 2.81; 95% confidence interval [CI], 1.47-5.39) [9]. The results of another

meta-analysis reported a 19-day delay in the diagnosis of TB because of empirical use of FQ for lower respiratory tract infection and that FQ exposure caused 2.7 times greater risk of resistance development than in patients without FQ exposure [5]. Animal studies also showed that FQ monotherapy caused resistant *M. tuberculosis* [20].

Another study on non-pulmonary TB reported delayed renal TB diagnosis and FQ resistance because of FQ monotherapy [21]. Increased risk is emphasized for multiple use, more than 10 days of use, and early stage use such as 2 or 3 months before the diagnosis [17, 22].

FQ exposure increases the risk of FQ resistance development, especially in patients infected with HIV and with low $CD4^+$ lymphocyte count or advanced immunosuppression [5, 11, 16, 17]. This problem is known to be more significant in areas where TB and HIV infections are endemic [23]. However, there are studies where no significant correlation has been shown between FQ exposure and FQ resistance. The authors state that empirical use of FQ does not lead to rapid development of FQ resistance and that FQ resistance is a problem which is more related to previous TB cases, particularly in patients with MDR TB [15, 24, 25]. Lee et al. [26] reported that no significant relationship was found between FQ use and FQ resistance in a cohort of patients with immunosuppressed TB, although they stated that the initiation of anti-TB treatment was significantly late in the FQ group.

Wang et al. [12] had reported that pneumonia was diagnosed within 6 months before the diagnosis of TB in 16,683 adult patients of 81,081 and that 2051 (12.3%) of these patients had more than 7 days of empirical FQ use. The authors stated that the initiation of anti-TB treatment had been delayed for 16.50 days in the FQ group ($p<0.001$) [12]. The varied results reported in the studies investigating the relation between FQ exposure and FQ resistance may be owing to methodological difference, number of patients, and patient selection.

This study had certain limitations, one of which was the retrospective study design. In addition, the incomplete use of prescribed drugs or use of unprescribed FQ and lack of sufficient information in the medical records could be considered as other limitations.

All FQs in addition to OFX and MFX were considered in this study. However, because FQ resistance in *M. tuberculosis* is related to gyrA and gyrB mutations in the bacteria genome, cross-resistance occurs between FQs. Cross-resistance between different FQs is highly common in *M. tuberculosis,* which could be explained by the association of resistance development in *M. tuberculosis* against potent bactericidal FQs with the development of additive mutations. Because the mechanism of resistance development is similar, and cross-resistance occurs in relation to this, the limitation that would arise from the differences between the FQs used is minimized in this study.

FQ resistance in *M. tuberculosis* is believed to be associated with more complex mechanisms (efflux mechanisms and so on) than what is known today [27, 28]. In patients suspected of having FQ resistance with phenotypical tests, *gyrA* and *gyrB* gene region mutations can be examined with molecular methods and DNA sequence analysis (sequencing). However, it is considered that there may be other mutations which cannot be detected by these methods; and therefore, advanced studies are required to investigate the mechanisms causing FQ resistance at the core of *M. tuberculosis*.

Hence, FQ exposure ratio before the diagnosis is high in patients with new case of active pulmonary TB. Although no statistically significant difference was found between FQ exposure and FQ resistance in the period before the diagnosis in this cohort, 2 new patients with FQ resistance were determined to have FQ exposure before the diagnosis. This can be interpreted as a cautionary result in terms of the correlation between FQ exposure and resistance development in *M. tuberculosis*. In cases where TB is considered during the differential diagnosis of lower respiratory tract infections, avoiding FQ monotherapy is important to prevent the selection of FQ-resistant strains.

Ethics Committee Approval: This single-center retrospective comparative case series study was approved by Health Sciences University Dr. Suat Seren Chest Diseases and Chest Surgery Training and Research Hospital review board (approval #326, dated 17/04/2013) and was carried out in accordance with the principles of the Helsinki Declaration.

Informed Consent: This case series study was performed retrospectively. Informations were obtained from medical records, pharmacy and Social Security Institution. Therefore, informed consent was not obtained from the patients.

Peer-review: Externally peer-reviewed.

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