Original Investigation

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Evaluating Fluoroquinolone Use in Patients Admitted to the Tuberculosis Outpatient Clinic

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Abstract

Objective: Inelaborate use of new quinolones with strong anti-tuberculosis (TB) activity leads to difficulty in diagnosis and more importantly, quinolone-resistant *Mycobacterium tuberculosis*. We aimed to determine the frequency of quinolone use in patients who were referred to our hospital for suspected TB and to evaluate the association between quinolone use and different clinical laboratory parameters.

Methods: Between November 15 and December 15, 2013, all patients who were admitted to the TB outpatient clinic with no previous diagnosis of TB were included in this study. Demographic and clinical laboratory findings and history of antibiotic use were recorded. Patients' quinolone use were questioned by showing fluoroquinolone antibiotic boxes' photographs available on the market. The departments of the doctors who prescribed quinolones were recorded.

Results: The mean age of 179 patients included in the study was 37±16 (15–89) years. Among these, 113 patients (63.1%) were male. Seventy five patients (41.9%) were diagnosed as tuberculosis according to the clinical-radiological and/or bacteriological findings. Of 179 patients, 58.1% (n=104) had been prescribed antibiotics for current complaints before referral to our clinic. Sixteen patients (15%) had been recommended fluoroquinolones. Fluoroquinolones were prescribed by seven internal medicine specialists, five pulmonologists, three emergency medicine specialists, and one family medicine practitioner. Among 16 fluoroquinolones prescribed, nine were moxifloxacin, four were levofloxacin, and three were gemifloxacin. Quinolone use revealed a significant inverse relationship only with the presence of hemoptysis (p=0.04).

Conclusion: Besides increased educational activities regarding the rational use of antibiotics in recent years, the quinolone group of antibiotics is still prescribed for suspected TB cases. To avoid quinolone-resistant *M. tuberculosis* strains, further education is required.

Keywords: Antibiotics, fluoroquinolones, infection, pneumonia, tuberculosis

INTRODUCTION

Tuberculosis (TB) is an infectious disease that constitutes a problem all over the world. The World Health Organization (WHO) publishes reports on fighting against the disease and its prevalence regularly. The last one was published in 2015 (1). According to this report, the incidence of TB is estimated to be 133/100000 globally and 18/100000 in Turkey. Compared to previous years, its incidence has decreased in Turkey, but an increase can occur in near future due to migration to Turkey. Early diagnosis and treatment and contact screening constitute the basis of the fight against TB. The treatment includes long-term multi-drug therapy and has not changed since the 1980s. Drug resistance is an expensive and difficult problem in the treatment of TB. The place of quinolones in TB treatment has been studied for a long time. In the study by Ruiz-Serrano et al. (2), the sensitivity of *Mycobacterium tuberculosis bacillus* to ciprofloxacin, ofloxacin, levofloxacin, grepafloxacin, trovafloxacin, and gemifloxacin was studied. In this study, while levofloxacin, ciprofloxacin, and grepafloxacin displayed very high efficiency and ofloxacin showed good efficiency, on the other hand, gemifloxacin and trovafloxacin showed low *in vitro* efficiency. At present, quinolones are routinely used in the treatment of multi-drug resistant tuberculosis (MDR-TB). In a recently published review, it has been reported that moxifloxacin is as bactericidal as first-generation tuberculosis drugs and this drug should be used

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in the treatment of MDR-TB routinely and it should be among the first choices for patients that can not tolerate standard treatment (3). There are ongoing studies on the inclusion of moxifloxacin in the standard treatment for shortening the duration of treatment (4-6).

In society, quinolones are commonly preferred due to their use as a single dose and their few side effects, especially in the treatment of pneumonia. However, this creates a risk for the development of resistance to quinolones in Turkey where TB is commonly seen. Some precautions for restricting the use of quinolones are taken in the Legal Notice of the Social Security Administration on the Implementation of Health. According to this notice, quinolones can be repaid only if they are prescribed based on the indication for pneumonia or based on consistent culture and antibiogram results. The efficiency of new quinolones in TB has been revealed (2-6). In Turkey, TB is endemic; therefore, quinolone should not be given to any patient who has the possibility for being diagnosed with TB. If a patient with TB is applied quinolone therapy, a clinical and radiological response can be obtained and bacteriological tests can be affected and this can cause delayed diagnosis (7, 8). Moreover, giving quinolone as a single therapy to a TB patient can lead to the development of resistance and further difficulties in the treatment of MDR-TB in the following years. In light of this knowledge, the aim of our study is to investigate the frequency of fluoroquinolone prescription in patients referred to a specific tuberculosis outpatient clinic of a chest diseases hospital by a physician due to suspected tuberculosis.

METHODS

The study included patients who were first admitted to the Tuberculosis Outpatient Clinic of İstanbul Yedikule Training and Research Hospital for Chest Diseases and Thoracic Surgery between November 15, 2013 and December 15, 2013. While patients that were previously diagnosed with TB and receiving treatment or coming for control despite having completed their treatments were excluded from the study, all new patients evaluated for the suspect of TB in our outpatient clinic were included. All patients included in the study were informed about the study and their informed consents were obtained. The study was conducted and written in accordance with the Declaration of Helsinki.

Our study was a cross-sectional study and the patients' ages, genders, complaints, their use of antibiotics for these complaints (if they used), the departments of the doctors who recommended that antibiotic therapy were recorded. Whether the antibiotic therapy given to the patient was included in the new quinolone group was questioned and the boxes of all fluoroquinolone antibiotics (levofloxacin, moxifloxacin, gemifloxacin) available on the market were shown to the patients. Each patient was asked about the way and duration of antibiotic use for confirmation. All the patients underwent chest radiography and analyses of sedimentation, hemogram, and C-reactive protein (CRP). The examination of acid-resistant bacilli (ARB) in smear and culture was performed at least twice in patients that could produce sputum. In patients who could not produce sputum, ARB examination was performed in bronchoscopic lavage. Other biochemical and computed tomographic examinations were carried out in indicated cases. In all the patients who could give sputum samples, direct smear and culture were examined together. The results obtained were recorded. The diagnosis of TB was established through the growth of *M. tuberculosis* in culture or the presence of ARB in sputum smear with clinical and radiological consistency despite the absence of growth in culture, or a clinically and radiologically made decision of TB despite 2 negative sputum smears taken at a 15-day interval. In cases not diagnosed bacteriologically, the patients whose diagnoses of TB were confirmed based on the anti-TB treatment responses in the first and second month control visits were included in the study. If there was no response or there was a progression, the diagnosis of TB was ruled out. At the end of the 2-month follow-ups of patients, the diagnosis of TB was grouped according to the evaluation of the hospital's archive.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (IBM SPSS Statistics for Windows, Version 22.0. IBM Corp, Armonk, New York, USA) software. Descriptive continuous values were presented as the mean (and standard deviation). Categorical variables were expressed as the number of cases and percentage value. The Shapiro–Wilk test was used for evaluating the consistency of normal distribution in continuously measured variables. Moreover, the Student's t-test and Mann–Whitney U test were employed for evaluating the continuous variables according to the situation of normal distribution or not. The comparison of categorical variables was performed by using Chi-square/Fisher's exact test. The value of $p<0.05$ was accepted to be statistically significant.

RESULTS

The study included 179 patients who had applied to the outpatient clinic of TB for the first time in a 1-month period. The mean age of these patients was 37±16 years (15–89 years). Of the cases, 113 (63.1%) were male. Sputum samples were taken from 125 patients and ARB smear was found to be positive in 35 patients. Seventy-five patients (41.9%) were clinically-radiologically or bacteriologically (ARB positive/culture positive) diagnosed with TB. The rate of positive ARB was detected to be 46.7% (n=35) in patients diagnosed with TB. Of TB patients with negative ARB smear, 31 (41.3%) were diagnosed through positive culture and 9 (12%) were diagnosed clinically and radiologically. The rate of TB patients who were diagnosed bacteriologically was 88% (n=66). Considering the complaints of all patients at admission, 40.2% had fever, 41.3% had weight loss, 57.5% had night sweating, and 26.3% had hemoptysis. Of 179 patients referred to the outpatient clinic of TB, 58.1% (n=104) had been given antibiotics due to their existent complaints before applying to our clinic. Sixteen (15%) patients having used antibiotics had been recommended to take new quinolone group antibiotics. Considering the branches of physicians who recommended new quinolones, 7 were internal medicine specialists, 5 were pulmonologists, 3 were emergency specialists, and 1 was a family medicine practitioner. The prescription rate of fluoroquinolone in patients with TB was 12% (9/75) [the rate was 8% if gemifloxacin is excluded (6/75)].

When the group having a history of antibiotic usage (n=104) was evaluated by itself, it was found that patients who were given new quinolone and patients who were started with a non-quinolone antibiotic were similar in terms of age, gender, ARB positivity, the rate of TB diagnosis, and the symptoms of fever, night sweating, and weight loss ($p>0.05$ for all parameters, Table 1). In the comparison carried out for detecting the presence of hemoptysis, it was found that new quinolones were more prescribed in patients without hemoptysis ($p=0.04$). Of the new quinolones that were used, 9 were moxifloxacin, 4 were levofloxacin, and 3 were gemifloxacin. Considering the indications for the prescription of new quinolones, it was found that

Table 1. Features of the groups according to the antibiotics used (n=104)

	Quinolone group (n=16)	Non-quinolone group (n=88)	p
Age (m±SD)	35±15	36±15	0.87
Male gender, n (%)	11 (68.8%)	53 (60.2%)	0.52
ARB positivity*, n (%)	2 (20%)	20 (22.7%)	0.52
Diagnosed with TB, n (%)	9 (56.3%)	44 (50%)	0.56
Presence of fever, n (%)	9 (56.3%)	43 (48.9%)	0.59
Night sweating, n (%)	9 (56.3%)	59 (67%)	0.40
Loss of weight, n (%)	6 (37.5%)	42 (47.7%)	0.45
Hemoptysis, n (%)	1 (6.3%)	28 (31.8%)	0.04

*There are 75 patients giving samples for ARB analysis
ARB: Acid-resistant bacilli; m±SD: mean±standard deviation; TB: tuberculosis

they were given for pneumonia in 15 patients and for pleurisy in 1 patient. With regard to the distribution of physicians prescribing the new quinolone group and other antibiotic groups, no significant difference was detected between the groups (p=0.54). TB was found in 9 (56.3%) of 16 patients who were recommended to use fluoroquinolone. The features of these patients are presented in Table 2 according to the presence of TB. Accordingly, no difference was found between the groups with and without TB in terms of symptoms, ARB positivity, and the type of quinolone (p>0.05 for all parameters, Table 2). Among patients applied with the complaint of hemoptysis, only 1 patient was prescribed a new quinolone, but this quinolone was moxifloxacin and was prescribed by a pulmonologist. In the quinolone group, TB was detected in 5 patients recommended to use moxifloxacin (55.6%), in 1 patient recommended to use levofloxacin (25%), and in all the patients (n=3) recommended to use gemifloxacin. No relationship was found between the selected fleuroquinolone and the diagnosis of TB (p=0.14). In patients diagnosed with TB, detailed information about the specialities of physicians that prescribed fluoroquinolones is given in Table 2.

Table 2. Demographic, clinical, and laboratory features of tuberculosis and non-tuberculosis patients using fluoroquinolone

	TB group (n=9)	Non-TB group (n=7)	p
Age (m±SD)	36±12	34±19	0.79
Male gender, n (%)	6 (66.7%)	5 (71.4%)	>0.99
ARB positivity*, n (%)	2 (22.2%)	0	0.23
Presence of fever, n (%)	7 (77.8%)	2 (28.6%)	0.13
Presence of night sweating, n (%)	5 (55.6%)	4 (57.1%)	>0.99
Presence of weight loss, n (%)	4 (44.4%)	2 (28.6%)	0.63
Presence of hemoptysis, n (%)	0	1 (14.3%)	0.44
The type of used quinolone, n (%)			0.14
Moxifloxacin	5 (55.6%)[1]	4 (57.1%)	
Levofloxacin	1 (11.1%)[2]	3 (42.9%)	
Gemifloxacin	3 (33.3%)[3]	0	

*There are 10 patients giving samples for ARB analysis in the group using quinolone.
The specialties of physicians that prescribed quinolones: 1Pulmonologist (n=2), [1]Emergency Physician (n=2), [1]Internal Medicine (n=1), [2]Family Medicine Physician (n=1), [3]Pulmonologist (n=1), [3]Internal Medicine (n=1), [3]Emergency Physician (n=1)
ARB: Acid-resistant bacilli; m±SD: mean±standard deviation; TB: tuberculosis

DISCUSSION

In our study, we investigated the frequency of new fluoroquinolone prescription in patients referred to a specific TB outpatient clinic of a chest diseases hospital by a physician due to suspected TB.

As a result of our study, it was found that the rate of fluoroquinolone prescription was 15% in cases with suspected TB and that the physicians who recommended these drugs were mostly internal medicine specialists and pulmonologists.

Turkey is a country where TB is endemic. Therefore, attention must be paid in the use of new quinolones, the efficiency of which have been proven in the treatment of TB, for the treatment of community-acquired infections. When a new quinolone is preferred for treatment in a case with suspected TB, clinical-radiological healing can be observed and bacteriological tests can be influenced. In such a situation, the diagnosis of TB can be delayed and resistance can develop against quinolone because quinolone was used as a single-drug treatment in a patient with TB (7, 8). Therefore, new quinolones should not be recommended in cases with suspected TB. Considering that physicians in 2 specialties (Respiratory Diseases and Internal Medicine) encounter tuberculosis cases more frequently and diagnose TB more often, it is clear that strict attention should be paid to the indications for quinolone use. Because the results of 3 major phase III studies on shortening the duration of treatment by adding a quinolone to TB treatment could not reveal the superiority of regimens with quinolones, there is no evidence for them to be included in routine standard treatment (9-11). Moreover, studies (STREAM and STAND studies) conducted for shortening the duration of treatment by adding new quinolones (particularly moxifloxacin) to MDR-TB therapy are ongoing. These studies suggest that new quinolones will have a more important place in the treatment of TB in the future.

According to annual WHO reports, the incidence of TB has decreased in Turkey and targets for TB control have been reached (1). However, there are some points that may entail a risk for this situation. The incidence of TB can increase due to migration to Turkey. Besides this, the use of new quinolones in society poses a threat for the control of MDR-TB and creates a risk for extensively-drug resistant TB (XDR-TB). Because quinolone resistance generally develops against a common part of the drug group, cross-resistance is frequently observed among quinolones (12-14). However, minimum inhibitor concentrations (MIC) of the new quinolones are lower compared to those of

the old quinolones. Therefore, the new quinolones may be effective on bacteria resistant to old quinolones such as ofloxacin (15-17). This should be kept in mind in the case of quinolone resistance because the choices in the treatment of resistant TB are restricted.

The use of respiratory quinolones in the treatment of community-acquired pneumonia in countries where tuberculosis is endemic can delay the diagnosis of TB (7, 8, 18). However, *in vitro* anti-TB efficiencies of quinolones differ from each other. For instance, for gemifloxacin, which is a fourth generation fluoroquinolone, to have wide antibacterial spectrum is typical. However, its *in vitro* efficiency for anti-TB is lower than that of moxifloxacin and levofloxacin (2, 19, 20). It can be said that gemifloxacin will not delay the diagnosis of TB considering its *in vitro* efficiency, but there are no sufficient studies on its *in vivo* efficiency and its clinical reflection. In the study by Kim et al. (21), 64 patients who had a TB diagnosis that was proven through culture and who had been given antibiotherapy due to the pre-diagnosis of community-acquired pneumonia before this diagnosis were evaluated. Among these patients, gemifloxacin, other fluoroquinolones, and non-fluoroquinolone antibiotics had been given to 16, 16, and 32 patients, respectively. While the median time passing from the initiation of gemifloxacin antibiotics to TB diagnosis was 9 days, this time was 35 days in the other fluoroquinolone group, which was significantly longer. This time was similar in the group using non-quinolone antibiotics and in the group using gemifloxacin. The rates of symptomatic and radiological healing were similar in the gemifloxacin and other fluoroquinolone groups, but it was reported that the frequency of radiological healing was higher in the other fluoroquinolone group than in the gemifloxacin group. Based on this result, it was concluded that gemifloxacin used in the treatment of pneumonia will not delay the diagnosis of TB. However, this study was retrospective and the number of patients included in the study might have been inadequate for revealing a statistical difference. Further comprehensive studies about the *in vivo* efficiency of gemifloxacin in TB and whether gemifloxacin causes delayed diagnosis of TB or not are needed. Besides this, 16 patients (15%) in our series were prescribed fluoroquinolone and 3 of them were given gemifloxacin. It is unknown whether low *in vitro* TB efficiency was known or not or if this was an incidental result while preferring gemifloxacin in these patients. In addition, despite the presence of hemoptysis, which is one of the symptoms more associated with TB and more striking, 1patient was given quinolone. The quinolone selected was moxifloxacin and was prescribed by a pulmonologist. This situation can be shown as a clear indicator of inadequate awareness on the use of quinolone.

In the study by Long et al. (22), which has some similar features to our study, the frequency of fluoroquinolone prescription, the types of drugs, and the number of drug cures were recorded from the files of 428 TB patients in the last 6 months. Quinolone resistances in the patients were compared. The rate of fluoroquinolone prescription in TB patients was found to be 17.3% (n=74), and this rate was 12% in our study (8% if gemifloxacin is removed). One of the results of this study was that the rate of quinolone resistance was 15% in patients prescribed quinolone more than once. This rate was significantly higher in patients given quinolone just once (0%) (odds ratio=11.4, p=0.04). However, when the limitations of this study were examined, the prescription of quinolones, like in our study, was evaluated, but it was observed that the duration of quinolone use was not specified clearly. The analysis was performed assuming that patients received their drugs and the development of resistance was evaluated. According to that, it was concluded that quinolone resistance did not develop as long as recurrent cures were not given to patients using quinolone. Moreover, smear positivity was found to be similar in groups given and not given quinolone (50% vs 40.5%). In our study, while ARB positivity was 2/9 (22.2%) in TB patients using quinolone, it was 20/44 (45%) in TB patients not taking quinolone (Table 1). This suggests that the use of quinolone can affect bacteriological tests, which is similar to the result of the study conducted by Wang (7) and Dooley et al. (8). However, the number of our patients was not sufficient for making an absolute judgment.

In our study, the use of antibiotics was investigated retrospectively. However, as in the study of Kim et al. (21), it did not provide any clinical data on whether quinolones would delay the diagnosis of TB or not, which is a limitation of our study. Moreover, there is no information about the duration of quinolone use in our study. This is because the analysis would not have provided reliable data on whether quinolones delayed TB diagnosis or not since we had only a few patients using quinolones in a 1-month period.

CONCLUSION

Our study was conducted for drawing attention to the frequency of new quinolone prescription in patients with suspected TB. This is the first original study on this subject because of the absence of any other study investigating the frequency of quinolone use in cases with suspected TB. On the other hand, there is a similar study evaluating the frequency of quinolone use in patients diagnosed with TB. New quinolones have an important place in the treatment of TB and it is suggested that they will contribute to shorter duration of TB treatments in the near future. While preferring new quinolone in community-acquired infections, particularly in pneumonias, we must think twice regarding preventing the development of resistance to new quinolones and we must avoid the use of quinolones in cases with suspected TB.

Ethics Committee Approval: Authors declared that the research was conducted according to the principles of the World Medical Association Declaration of Helsinki "Ethical Principles for Medical Research Involving Human Subjects", (amended in October 2013).

Informed Consent: Verbal informed consent was obtained from patients who participated in this study.

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