MAJOR ARTICLE

Empirical Treatment of Community-Acquired Pneumonia and the Development of Fluoroquinolone-Resistant Tuberculosis

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(See the editorial commentary by Low on pages 1361–3)

Background. Fluoroquinolone (FLQ) antibiotics are not uncommonly prescribed for community-acquired pneumonia that is later proven to be pulmonary tuberculosis (TB). Such FLQ monotherapy may result in FLQ-resistant pulmonary TB.

Methods. To assess outpatient FLQ use by patients with culture-proven pulmonary TB before diagnosis, TB registries in Alberta and Saskatchewan, Canada, were linked with provincial and federal drug benefit plans. To assess FLQ resistance, a case-control study was performed.

Results. Of 428 patients with pulmonary TB who were covered by a drug benefit plan, 74 (17.3%) had received ⩾1 FLQ prescription during the 6 months immediately before receipt of the diagnosis. Older patients (age, >64 years) were more likely than younger patients (age, 15–64 years) to be prescribed an FLQ ($P < .05$). Patients who were prescribed an FLQ received a total of 103 prescriptions. Most (54 [73.0%] of 74) patients who were prescribed an FLQ received a single prescription. Most (69 [67.0%] of 103) FLQ prescriptions were written within 90 days before the diagnosis of pulmonary TB. Patients who were prescribed an FLQ were not statistically significantly more likely than matched patients who were not prescribed an FLQ (control subjects) to be infected with FLQ-resistant *Mycobacterium tuberculosis*. Of 148 isolates of *M. tuberculosis* from patients and control subjects, 3 were FLQ resistant; all of these isolates were from patients who had received multiple FLQ prescriptions. Patients who had received multiple FLQ prescriptions were more likely than patients who had received a single FLQ prescription to be infected with FLQ-resistant *M. tuberculosis* (15.0% vs. 0.0%; odds ratio, 11.4; $P = .04$).

Conclusions. Outpatient FLQ use, ostensibly for community-acquired pneumonia, is not uncommon among patients with pulmonary TB, especially older patients. Single FLQ prescriptions were not associated with FLQ-resistant *M. tuberculosis,* whereas multiple FLQ prescriptions were associated with FLQ resistance.

Fluoroquinolones (FLQs) are emerging as important drugs for the treatment of multidrug-resistant tuberculosis (TB) and for the treatment of TB in patients who are intolerant of standard therapy [1, 2]. New FLQs, particularly the 8-methoxy FLQs moxifloxacin and gatifloxacin, also promise to shorten the duration of TB treatment [3, 4]. Before a definitive diagnosis of pulmonary TB is made, a patient may mistakenly receive a diagnosis of community-acquired pneumonia (CAP) and, pursuant to recommendations for the treatment of CAP, may be prescribed an FLQ antibiotic [5]. Under such circumstances, an FLQ may produce a favorable short-term response, because the FLQs have good in vitro and in vivo activity against *Mycobacterium tuberculosis.* However, FLQ monotherapy for CAP that is, in fact, pulmonary TB is fraught with problems. These include a delayed diagnosis of pulmonary TB, with an attendant increase in severity, mortality, and transmission, and an increase in the risk of development of FLQ-resistant TB [6–9]. Use of a single drug to treat active pulmonary TB may result in the selection

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of naturally occurring resistant mutants, resulting in the drug—in the case of FLQs, the class of drugs—no longer being effective [10].

The FLQs were first introduced in clinical practice in the 1980s. Because FLQs have broad-spectrum antimicrobial activity, they have been recommended and widely used for the treatment of bacterial infections of the respiratory, gastrointestinal, and urinary tracts, as well as for the treatment of sexually transmitted diseases and chronic osteomyelitis [9]. Their high level of oral bioavailability, relative absence of hepatotoxicity, and excellent safety record in long-term therapy make FLQs especially attractive for the treatment of TB [9]. In addition, there is no cross-resistance between FLQs and other anti-TB drugs [9]. In Alberta, Canada (population [2001 census], 2,941,150), FLQs accounted for ~6% and ~12% of all antibiotic prescriptions in 1999 and 2006, respectively [11]. In this study, we identified patients with pulmonary TB who were covered by a drug benefit plan and who had been prescribed an FLQ during the 6 months before the diagnosis of pulmonary TB. The initial isolates of *M. tuberculosis* from patients who had received FLQ treatment and from a matched control group of patients with pulmonary TB who had not received FLQ treatment were tested for FLQ resistance.

METHODS

To select a study population of patients who were covered by a drug benefit plan, all adults (age, >14 years) who received a diagnosis of culture-proven pulmonary TB in Alberta (all population groups) and Saskatchewan (Status Indians) from July 1996 through December 2003 were identified in their respective TB registries and were linked (by name, date of birth, and personal health care number) with the 2 major drug benefit plans available to them (Alberta Health and Wellness and First Nations and Inuit Health). A drug benefit plan is an insurance plan that includes the costs of outpatient prescription drugs. Status Indians are First Nations persons who are registered in accordance with the terms of the Indian Act of Canada.

Data abstracted from the plans included whether and when an FLQ prescription had been written, the type of FLQ prescribed, and the duration of each FLQ prescription during the 6 months immediately preceding the date of diagnosis of pulmonary TB (the start date of anti-TB drug treatment). Only outpatient prescriptions (the drug benefit plans did not cover prescriptions written for hospitalized patients), prescriptions written before the collection of the specimen that grew the archived isolate of *M. tuberculosis,* and prescriptions for an oral FLQ were included. Patients with pulmonary TB who had received an FLQ were compared with patients with pulmonary TB who had not received an FLQ with regard to age, sex, population group, disease type (new active vs. relapse), cavitation on chest radiograph, first-line anti-TB drug resistance, and HIV status. In addition, patients who had received multiple ($\geqslant$2) prescriptions were compared with those who had received a single prescription for the same variables.

To evaluate the association between FLQ-resistant pulmonary TB and prior FLQ use, we performed a case-control study. For each patient with pulmonary TB and a history of FLQ use, a control subject was selected at random from a pool of patients who had not received FLQ treatment and was matched by age ($\pm$5 years), sex, population group, and province of residence. Matched-control selection was performed using the sample function without replacement in SPSS, version 13.0 (SPSS). Archived isolates of *M. tuberculosis* from patients and control subjects (the first isolate to grow in connection with an incident episode) were tested in the Provincial Reference Laboratory (Edmonton, Alberta, Canada) for in vitro susceptibility to ciprofloxacin, ofloxacin, and levofloxacin. Laboratory staff were blinded to the FLQ prescription history. Testing was performed by the indirect proportion method with use of the following drug concentrations: ciprofloxacin, 0.5, 1.0, 2.0, and 4.0 μg/mL; and ofloxacin and levofloxacin, 1.0, 2.0, 4.0, and 8.0 μg/mL. Drug resistance was defined as an MIC >2.0 μg/mL for ciprofloxacin and ofloxacin and an MIC >1 μg/mL for levofloxacin [12–14]. Resistance to ofloxacin was confirmed using the agar proportion method [15]. For FLQ-resistant isolates and a sample of FLQ-susceptible isolates, detection of mutations responsible for resistance was performed in the National Mycobacteriology Laboratory (Winnipeg, Manitoba, Canada) by PCR amplification and sequencing of genes encoding gyrase A and B [16–18]. In addition, patients who had received multiple prescriptions for FLQs were compared with patients who had received a single prescription for FLQ with respect to the frequency of FLQ-resistant pulmonary TB.

The χ^2 test was used for analysis of differences in the demographic characteristics of patients with pulmonary TB who were from Alberta and were or were not in a drug benefit plan. Multiple logistic regression analysis was used to determine the association between receipt of an FLQ and the demographic and clinical characteristics of patients with pulmonary TB. Fisher's exact test was used to test differences in proportions when the expected values were <5. The OR and level of significance (P value) for the association between FLQ resistance and the number of FLQ prescriptions was determined using exact logistic regression. This study was approved by the Ethics Boards of the Universities of Alberta and Saskatchewan.

RESULTS

During the study period, 731 adults received a diagnosis of culture-positive pulmonary TB; 563 of these patients were from Alberta (all population groups), and 168 were from Saskatchewan (Status Indian). Of the 731 patients with pulmonary TB, 428 (58.5%) were covered by a drug benefit plan. Among the

patients from Alberta, a greater proportion of older patients (age, >64 years) than younger patients (age, 15–64 years; $P < .001$) and a greater proportion of Status Indians than Canadian-born patients who were not Status Indian ($P < .001$) and foreign-born patients were covered by a drug benefit plan (data not shown; $P < .001$).

Of the 428 patients with pulmonary TB who were covered by a drug benefit plan, 74 (17.3%) had received ⩾1 FLQ prescription. In univariate logistic regression analysis, patients who were prescribed an FLQ were more likely to be older (age, >64 years; $P = .001$), less likely to be Status Indian than to be Canadian-born and not Status Indian ($P < .05$), and less likely to have cavitary disease ($P < .05$), compared with patients who were not prescribed an FLQ (table 1). In multivariate logistic regression analysis, only the difference in age between the patients who received an FLQ and those who did not was statistically significant ($P < .05$). The proportion of older Status Indians, Canadian-born persons who were not Status Indian, and foreign-born persons who were prescribed an FLQ was similar (22.9%, 26.3%, and 23.3%, respectively). From 1996 through 2003, the median proportion of patients who were prescribed an FLQ was 17.8% (range, 9.1%–21.5%). The 74 patients who were prescribed an FLQ had received a total of 103 prescriptions; 54 had received single prescriptions, and 20 had received multiple prescriptions. In univariate logistic regression analysis, patients who had received multiple prescriptions of FLQs were more likely than those who had received a single prescription of an FLQ to be Status Indian than to be Canadian-born and not Status Indian ($P < .05$) and to be infected with *M. tuberculosis* with drug resistance to first-line treatment than to be infected with drug-susceptible *M. tuberculosis* (data no shown; $P < 0.05$). No patient or control subject had multidrug-resistant TB. Of the 103 FLQ prescriptions, 16 (15.5%) were for norfloxacin, 70 (68.0%) were for ciprofloxacin, 3 (2.9%) were for ofloxacin, 13 (12.6%) were for levofloxacin, and 1 (1.0%) was for moxifloxacin.

The selection of study patients and the outcome of drug susceptibility testing are summarized in figure 1. Case patients were not more likely than control subjects to have FLQ-resistant TB ($P = .25$). FLQ resistance was limited to patients who had

Table 1. Demographic and clinical characteristics of patients with pulmonary tuberculosis (TB) who had and had not received a fluoroquinolone (FLQ) prescription, July 1996–December 2003.

Characteristic	No. (%) of patients with culture-positive pulmonary TB		OR (95% CI)	
	No FLQ prescription ($n = 354$)	⩾1 FLQ prescription ($n = 74$)	Univariate analysis	Multivariate analysis
Age, years				
15–64	200 (56.5)	26 (35.1)	1.00	1.00
>64	154 (43.5)	48 (64.9)	2.40[a] (1.42–4.04)	2.20[b] (1.08–4.49)
Sex				
Female	157 (44.4)	40 (54.1)	1.00	…
Male	197 (55.6)	34 (45.9)	0.68 (0.41–1.12)	…
Population group				
Canadian-born (not Status Indian)	30 (8.5)	11 (14.9)	1.00	1.00
Status Indian	224 (63.3)	35 (47.3)	0.43[b] (0.20–0.93)	0.76 (0.31–1.91)
Foreign-born	100 (28.2)	28 (37.8)	0.76 (0.34–1.71)	0.76 (0.34–1.72)
Disease type				
New active	307 (86.7)	65 (87.8)	1.00	…
Relapse	47 (13.3)	9 (12.1)	0.90 (0.42–1.94)	…
Cavitary disease				
No	255 (72.0)	62 (83.8)	1.00	1.00
Yes	99 (28.0)	12 (16.2)	0.50[b] (0.26–0.97)	0.54[c] (0.27–1.04)
Drug resistance[d]				
No	339 (95.8)	71 (95.9)	1.00	…
Yes	15 (4.2)	3 (4.1)	0.96 (0.27–3.39)	…
HIV status				
Negative or unknown	349 (98.6)	72 (97.3)	1.00	…
Positive	5 (1.4)	2 (2.7)	1.94 (0.37–10.19)	…

[a] $P = .001$.
[b] $P < .05$.
[c] $P = .07$.
[d] To first-line drugs; isolates from Saskatchewan were not tested for pyrazinamide resistance.

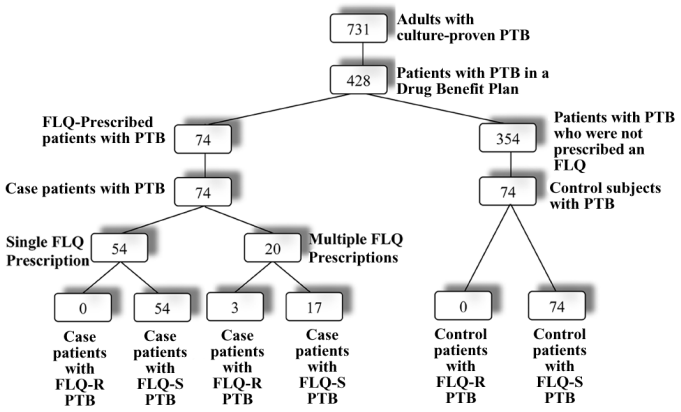

Figure 1. The selection of study patients and the outcome of fluoroquinolone (FLQ) drug susceptibility testing. Because of a limited number of potential control subjects, the criteria for matching had to be expanded in 4 instances. Of these, 2 case-control pairs were matched by age to within 10 years, one pair was matched by age to within 15 years, and the last pair was not matched by sex. Of the 74 patients who had received an FLQ prescription, 73 had complete (180 days) drug benefit coverage, and 1 (a patient who had received a single FLQ prescription) had incomplete (90 days) drug benefit coverage. All control subjects had complete drug benefit coverage. PTB, pulmonary tuberculosis; R, resistant; S, susceptible.

received multiple FLQ prescriptions. Patients who had received multiple FLQ prescriptions were more likely than patients who had received a single FLQ prescription to have FLQ-resistant TB (15.0% vs. 0.0%; OR, 11.4; $P = .04$). Compared with patients who had received a single FLQ prescription, patients who had received multiple FLQ prescriptions received a longer total median duration of FLQ treatment before the collection of the specimen that grew the archived isolate of *M. tuberculosis* (16 days [range, 8–43 days] vs. 7 days [range, 1–14]; $P < .001$). All patients with FLQ-resistant TB were >64 years of age and had positive smear results. Two patients with FLQ-resistant TB had new active TB, and 1 patient had a relapse of pulmonary TB; of these 3 patients, 2 were HIV uninfected, and 1 had an unknown HIV status. FLQ exposure did not affect the smear status of patients; 37 patients (50.0%) and 30 control subjects (40.5%) were smear positive.

The MICs for all FLQs tested were increased (table 2). Only one isolate had a resistance-conferring mutation in the *gyr*A gene. This isolate came from an HIV-uninfected patient (patient 2). There were no *gyr*B mutations in the FLQ-resistant isolates and no *gyr*A or *gyr*B mutations in 6 sample FLQ-susceptible isolates. FLQ-resistant isolates were from patients who had received multiple ciprofloxacin treatments (the durations of treatment in patient 1 were 7 and 10 days, in patient 2 were 7 and 7 days, and in patient 3 were 14 and 10 days).

FLQ prescription dates, relative to the date of diagnosis of pulmonary TB, are depicted graphically in figure 2. The median time from the last FLQ prescription to the date of diagnosis was 42 days (range, 2–172 days). Most FLQ prescriptions (69 [67.0%] of 103) were written within 90 days of the date of diagnosis of pulmonary TB.

DISCUSSION

In contrast to most other drugs used to treat CAP, the FLQs have good activity against TB; in contrast to most other drugs used to treat TB, the FLQs have good activity against CAP. In the present study, performed in a setting where the incidence of TB is low and the prevalence of HIV infection is low, we found that FLQ monotherapy, ostensibly for suspected CAP, was prescribed to 17.3% of all patients with pulmonary TB and 23.8% of older patients (age, >64 years) with pulmonary TB during the 6 months immediately before receipt of the diagnosis. Most patients (73.0%) who had been prescribed an FLQ had received a single prescription; most FLQ prescriptions (67.0%) were written within 90 days before the diagnosis of pulmonary TB. Multiple, but not single, FLQ prescriptions were associated with FLQ resistance. As reported elsewhere, *gyr*A mutations did not explain FLQ resistance in all isolates [9].

Our study population—adult patients with pulmonary TB who were covered by a drug benefit plan—was, as expected, skewed toward older patients (age, >64 years) and Status Indians; insured services beyond Medicare are regularly provided by the government to older persons and to Status Indians. The proportion of patients with pulmonary TB who had been prescribed an FLQ (17.3%) was similar to that reported by Gaba et al. [19] (23.0%) in the only comparable study of outpatient FLQ use that involved patients with TB. That study examined all patients with TB in a drug benefit plan, regardless of disease type or bacillary status, and included patients whose coverage extended to ⩾300 days during the year preceding TB diagnosis. Gaba et al. [19] also found that older patients were more likely to be prescribed an FLQ, a finding that is consistent with the

Table 2. Drug susceptibility and DNA gyrase test results for fluoroquinolone (FLQ)–resistant *Mycobacterium tuberculosis* isolates.

	First-line drugs (indirect proportion)					FLQs				DNA gyrase mutation	
						Indirect proportion MIC, μg/mL			Agar proportion MIC, μg/mL		
Patient	INH	RIF	PZA	EMB	SM	CIP	OFL	LEV	OFL	*gyr*A	*gyr*B
1	R	…	…	…	…	⩾ 4.0	⩾ 8.0	⩾ 8.0	⩾ 8.0	…	…
2	…	…	…	…	…	8.0	⩾ 4.0	8.0	8.0	A90V	…
3[a]	R	…	…	…	R	4.0	4.0	2.0	2.0–4.0	…	…

NOTE. CIP, ciprofloxacin; EMB, ethambutol; INH, isoniazid; LEV, levofloxacin; OFL, ofloxacin; PZA, pyrazinamide; R, resistance; RIF, rifampin; SM, streptomycin.

[a] Patient 3 experienced a relapse of pulmonary tuberculosis. The patient's first episode occurred in 1958. At that time, the initial isolate of *M. tuberculosis* was susceptible to INH, paraaminosalicylic acid, and streptomycin.

altered presentation of pulmonary TB (fewer patients with cavitary disease or a positive tuberculin test result) and the greater likelihood of comorbidities in this age group [19–22]. Current guidelines for the outpatient treatment of CAP recommend an FLQ for patients with comorbidities but not for patients who were previously healthy, have not received antimicrobials during the previous 3 months, or have other risk factors for drug-resistant *Streptococcus pneumoniae* infection [5]. Although the overall frequency of FLQ use increased over time in the jurisdiction of our study, the frequency of FLQ use for the treatment of pneumonia [11] and by patients with pulmonary TB did not increase.

In our study, patients who had been prescribed an FLQ were not statistically significantly more likely than patients who had not been prescribed an FLQ to have FLQ-resistant TB. However, all patients with FLQ-resistant TB had received not just one but multiple FLQ prescriptions. Although multiple prescriptions or longer exposure times were not associated with FLQ resistance in a study from Taiwan, experience with isoniazid suggests that exposure time is indeed important [10, 22]. When isoniazid monotherapy was given to treat either TB disease or latent TB infection, the rates of isoniazid resistance were 26.7%, 48.4%, and 64.7% among those receiving isoniazid for <2 weeks, 2 weeks–1 month, and 1–6 months, respectively [10]. The usual duration of a single FLQ treatment regimen for CAP is 5–10 days [5]. The absence of FLQ resistance in patients

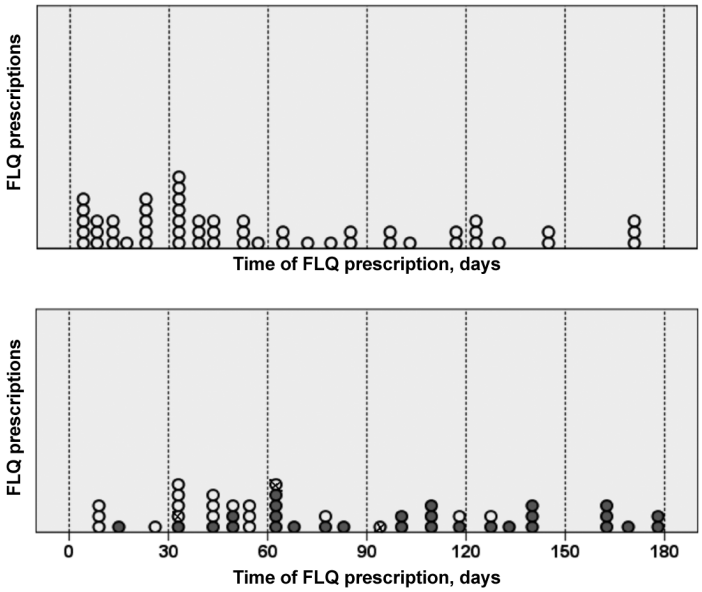

Figure 2. Time from receipt of a fluoroquinolone prescription (FLQ) to diagnosis of tuberculosis (time 0) for patients who had received a single FLQ prescription *(top; n* = 54) and for patients who had received multiple FLQ prescriptions (*bottom; n* = 20). White circles indicate the prescription closest to the diagnosis for patients with FLQ-susceptible TB, circles with an "x" indicate the prescription closest to the diagnosis for patients with FLQ-resistant TB, and black circles indicate earlier FLQ prescriptions in patients who had received multiple FLQ prescriptions.

with pulmonary TB who had received a single FLQ prescription suggests that FLQ exposures of this duration are unlikely to induce FLQ resistance.

Several studies have associated FLQ resistance with first-line anti-TB drug resistance (especially multidrug-resistant TB) and prior treatment of TB [14, 22, 23–31]. In our study, we could not disassociate FLQ resistance from first-line drug resistance; more patients who had received multiple FLQ prescriptions than patients who had received a single FLQ prescription had TB with first-line drug resistance. Other factors have been implicated in the development of FLQ resistance, including proximity of FLQ exposure to the date of TB diagnosis, high bacillary burden, and HIV infection [8, 14, 24, 28, 32]. One or more of these factors may have been operative in a case of FLQ-resistant TB that developed after 7 days of FLQ exposure and in another case that developed after 13 days of exposure [8, 32].

There are some obvious shortcomings of our study. First, although our study included FLQ use by nonhospitalized emergency department attendees (an important group, given the frequent use of emergency departments by patients with TB and FLQ prescribing practices within emergency departments), it did not include in-hospital FLQ use [33, 34]. Second, we presupposed that patients who had been prescribed an FLQ actually took their medication. In the first instance, FLQ exposure and FLQ resistance might have been underestimated; in the second, it might have been overestimated. Third, we assumed that FLQ prescriptions were for treatment of suspected CAP, when some prescriptions, such as those for norfloxacin, may have been for treatment of non-CAP disease. Prescriptions for treatment of non-CAP disease would have inflated the estimated proportion of patients with pulmonary TB who were suspected of having CAP.

In summary, despite the not uncommon use of FLQs during the months immediately preceding the diagnosis of pulmonary TB, FLQ resistance is uncommon, occurring in patients who have received multiple FLQ prescriptions, in patients who are being retreated, and in patients with first-line drug-resistant TB. Indiscriminate use of FLQs, especially in developing countries, and the use of FLQs in the World Health Organization and International Union against Tuberculosis and Lung Disease diagnostic algorithm are discouraged [35]. Vigilance for pulmonary TB needs to be maintained. Increased diagnostic testing needs to be considered when patients have risk factors for TB or infections due to other pathogens that are not adequately covered by empirical treatment regimens.

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