ORIGINAL ARTICLE

RAMR 2018;2:116-120
ISSN 1852 - 236X

Indications and safety profile of fluoroquinolones in the treatment of tuberculosis in a general hospital of the Autonomous City of Buenos Aires

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Abstract

Introduction: Fluoroquinolones are frequently used in treatment regimes for tuberculosis both in cases of multidrug-resistant tuberculosis, where they are an essential part of the regime, and also in cases of drug-sensitive tuberculosis with intolerance to first-line drugs.

Objectives: To evaluate indications to include fluoroquinolones in the anti-tuberculosis treatment and to describe the adverse events associated with their use.

Materials and Methods: A retrospective analysis of the patients who began treatment for tuberculosis between January 1, 2014 and December 31, 2016 was performed. We defined an adverse event as the condition that resulted in the suspension of a drug or the need to use specific drugs for its management. Group characteristics were compared by using the χ^2 test.

Results: Of the 267 patients who began treatment in said period, 24 (11 men) received fluoroquinolones, representing 9% of the total population; 19 were treated with 400 mg/day of moxifloxacin and the rest with 750 mg/day of levofloxacin. In the comparison of the groups receiving fluoroquinolones versus the ones without fluoroquinolones, there were no significant differences in the percentage of male participants (46 vs. 58%), age (34.7 ± 12 vs. 35.1 ± 15 years), pulmonary involvement (58 vs. 68%) and withdrawal rate (26 vs. 21%). There was a higher proportion of Argentinians (71 vs. 44%, p = 0.012) and of HIV-positive individuals (46 vs. 8.6%) p < 0.05) in the group with fluoroquinolones vs. the group without fluoroquinolones. Fluoroquinolones were indicated in replacement of rifampicin in 9 patients (37.5%) due to its interaction with antiretroviral drugs, in 9 patients (37.5%) due to intolerance, and in 5 patients (21%) due to resistance to first-line anti-tuberculosis drugs. In one individual, fluoroquinolones were indicated instead of pyrazinamide due to history of cirrhosis. The time of treatment with fluoroquinolones was 203 ± 158 days (range 30-660) with no observed adverse events related to their use.

Conclusion: In the group under study, the use of fluoroquinolones was not associated with adverse events. The most frequent indications in these patients were drug interactions in HIV-positive patients and intolerance to first-line drugs.

Key words: tuberculosis, fluoroquinolones, adverse events, moxifloxacin, levofloxacin

Introduction

Tuberculosis (TB) is a contagious infectious disease caused by the *Mycobacterium tuberculosis*. The World Health Organization estimates that one third of the world population is infected but without clinical manifestation (latent TB), and 10% will develop the disease[1].

The treatment regimes include several drugs considered first-line drugs (isoniazid, rifampicin, ethambutol, pyrazinamide) and the treatment is extended for 6 months or more in cases of drug-sensitive TB (according to the extension, site of infection, comorbidities), favouring the appearance of adverse events associated with these drugs[2]. In this situation, the fluoroquinolones (FQ) have been progressively and increasingly included given their effective early bactericidal activity against *Mycobacterium*

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tuberculosis, in replacement of first-line drugs in cases of intolerance[3], and because, on the other hand, they are also an essential pillar of the treatment of multidrug-resistant TB (MDR-TB). FQ prevent the synthesis of bacterial DNA from DNA gyrase inhibition. The specific adverse events are musculoskeletal disorders and QT interval prolongation[4]. Various studies including the safety analysis state that toxicity levels in treatment regimes with FQ are not higher than those of most common regimes, and FQ are frequently used in patients with liver failure or hepatotoxicity associated with first-line drugs[4-7].

The purpose of this study was to evaluate the inclusion of new globally used FQ (moxifloxacin and levofloxacin) in the treatment of patients with TB in a General Hospital, assessing the indications that promote their use and describing the adverse events.

Materials and Methods

We included patients diagnosed with TB, evaluated in a general hospital of the Autonomous City of Buenos Aires, who began their treatment between January 1, 2014, and December 31, 2016. We reviewed the medical records of every patient in order to obtain demographic data, comorbid conditions, TB site of infection and drug sensitivity pattern, if any. In cases where treatment with FQ was indicated, we evaluated the reason for such indication, the duration of the treatment and the presence of FQ-related adverse events. In our study, we define the adverse event as the condition that determines the suspension of the drug involved or the need to use specific drugs to manage such condition, excluding mild and self-limited reactions which wouldn't have otherwise modified the therapeutic regime.

In our Center we use the self-administered anti-TB treatment regime, with clinical control once a week during the intensive phase (the first 2 months), and then controls are carried out once a month. Lab tests are conducted at baseline, after one month and then once every 2 months, with modifications depending on the presence of symptoms or comorbidities. No routine electrocardiogram was performed in patients under treatment with FQ.

For the descriptive analysis we estimated the central tendency and dispersion measurements expressed as mean ± standard deviation for numerical variables and percentages for categorical variables. We used the χ^2 test and the Fisher's exact test for group comparisons of qualitative variables and the t test for the comparison of quantitative variables. A value of $p < 0.05$ was considered as statistically significant.

Results

We included 267 patients (152 men, 57%), age 35 ± 15 years, Argentinians 124 (46%). Most of the foreigners were Bolivian (n= 117.44% of all the patients). 180 out of the 267 participants had pulmonary TB (67%). The most frequently found comorbidities were: HIV-positive (n = 32.12%), alcoholism (n = 24.9%), and drug addiction, excluding smoking and diabetes. 24 (9%) patients of the total population received FQ, whether from the beginning or during the anti-TB treatment.

Table 1 shows the comparison between groups who received FQ and those who did not. But, with no difference as regards age, gender and site of infection, we observe a significantly higher amount of HIV-positive patients in the groups treated with FQ and in Argentinians. Although there has been a tendency to a greater proportion of HIV-positive patients among Argentinians, in comparison with foreigners (20/124 [16%] vs. 12/143 [8.4%]), this difference did not reach a statistical significance level (p= 0.052).

Patients treated with FQ **(Table 2)** received moxifloxacin, at a dose of 400 mg/day in 19 cases, and the rest were treated with levofloxacin, at a dose of 750 mg/day (no adjustment was made based on weight).

To 9 HIV-positive patients we administered FQ instead of rifampicin, due to its interaction with antiretroviral treatment (ART). These patients were receiving treatment regimes that included protease inhibitors (with history of failure with alternative regimes), and rifabutin is not always available to replace rifampicin. In one patient, due to his/her history of cirrhosis and elevated transaminases in the basal lab tests, we decided to use a less hepatotoxic regime, replacing pyrazinamide for moxifloxacin. FQ were included in the treatment of patients with MDR-TB (n = 4) and mono-resistant patients (n = 1,

TABLA 1. Comparison between the group that received fluoroquinolones and the group that did not receive fluoroquinolones

	Without FQ	With FQ	p value
N° of patients	243	24	
Age (years)	35.1 ± 15	34.7 ± 12	0.9
Men	141 (58%)	11 (46%)	0.2
Comorbidities			
HIV	21 (8.6%)	11 (46%)	p < 0.05
Alcoholism	21 (8.6%)	3 (12.5%)	0.5
Diabetes	14 (15.7%)	0	p = NS
Use of drugs	16 (6.6%)	0	p = NS
Other	73 (30%)	7 (29%)	0.9
Site of infection			
Pulmonary	166 (68%)	14 (58%)	0.3
Extrapulmonary and Mixed	73 (32%)	10 (42%)	0.3
Nationality			
Argentina	107 (44%)	17 (71%)	0.012
Bolivia	114 (47%)	3 (12.5%)	0.001
Other	22 (9%)	4 (16.5%)	0.23
Tx withdrawal	42 (21%)	5 (26%)	0.19

Abbreviations: FQ, fluoroquinolones; Tx, treatment

isoniazid). In the remaining 9 patients, FQ were indicated due to first-line drug intolerance: hepatotoxicity (n = 6.4 for pyrazinamide; 1 for rifampicin and 1 for isoniazid), thrombocytopenia (n = 2, for rifampicin) and polyneuropathy (n = 1 for isoniazid).

The average treatment duration with FQ was 203 ± 158 days (range 30-660) and except for one case, FQ were used for ≥ 60 days.

We did not register any adverse events related to the use of FQ that motivated the modification of the therapeutic regime or the need to administer a specific treatment. There weren't any significant differences in treatment withdrawals among the patients, whether they received FQ or not.

Discussion

In this study we showed the safety profile and indications for FQ in a group of patients with TB treated in a General Hospital of the Autonomous City of Buenos Aires.

We observed that FQ were included in the treatment of 9% of the total population of TB patients treated in our center; the most frequent indications being intolerance to anti-TB first-line drugs and the interaction of rifampicin with antiretroviral drugs used in HIV patients (when rifabutin was not available). Rifampicin is an inductor of several isoenzymes of the cytochrome P450 system (such as protease inhibitors and non-nucleoside reverse transcriptase inhibitors used in HIV patients[8]), and reduces the serum levels of many drugs to subtherapeutic values. In our hospital we do not always have other rifamycins to replace rifampicin. So, we replaced rifampicin for FQ in cases of HIV-positive patients unable to receive a dose regime with efavirenz, where it has been proven that coadministration of rifampicin does not reduce the efficacy of the antiretroviral treatment.

TABLA 2. Characteristics of patients treated with FQ

	Total	Levofloxacin	Moxifloxacin	
Nº of patients	24	5	19	
Age (years)	34.7 ± 12	26.8 ± 8	36.7 ± 12	p = 0.10
Men	11	1	10	
Nationality				
Argentina	17	3	14	
Bolivia	3	1	2	
Other	4	1	3	
Indication of FQ				
Intolerance to anti-TB	9	2	7	
Resistence to anti-TB	5	1	4	
Interactión with ART	9	2	7	
Comorbidities (cirrhosis)	1	0	1	
Tx days	203 ± 158	312 ± 71	194 ± 135	p = 0.07
Withdrawals	5	0	5	

Abbreviations: FQ, fluoroquinolones; ART, antiretroviral treatment; TB, tuberculosis; Tx, treatment.

Several studies conclude that the most frequent indication for FQ in patients with drug-sensitive TB is associated with intolerance to first-line drugs[6, 7]. Unlike two studies that describe rifampicin[7] and ethambutol[9] as the drugs causing the adverse events, in our population, hepatoxicity by pyrazinamide was the most frequently found event. These studies do not describe the use of FQ associated with antiretroviral drugs interaction (one of them was developed in South Korea, where the incidence of HIV is very low: only 1 patient out of 226 treated with FQ was HIV-positive).

In the group of patients under study, we did not find adverse events associated with FQ. One study including 226 patients who received FQ during an average of 275 days (moxifloxacin n = 122, levofloxacin n = 82, ofloxacin n = 22) only registered 2.2% of patients with adverse events related to the use of these antibiotics, mainly gastrointestinal alterations and allergic reactions. A prospective clinical study using moxifloxacin in the first phase of treatment[6] (instead of ethambutol), does not describe associated events or electrocardiographic changes (QT prolongation). A Cochrane meta-analysis[1] with 1330 patients of 5 randomized and controlled studies including FQ in the treatment of drug-sensitive TB replacing ethambutol or isoniazid did not find in any of the analyzed studies, specific adverse events related to the use of FQ, such as tendon inflammation or rupture and arrhythmias (associated with QT prolongation). Major hepatotoxicity isn't described, either, in FQ-containing regimes (particularly, moxifloxacin), in comparison with the common anti-TB treatment. However, in a study of 75 patients treated with moxifloxacin[10] and monitored by ECG, there were 16 cases of drug suspension (21.3%), with QT prolongation, arthralgias, allergy, insomnia, nausea, vomiting, angioedema and neutropenia. It should be noted that there was a high mean age among the patients (69.4 years) and 88% of comorbidities, which could explain the higher incidence of adverse events found in this population.

Conclusion

We conclude that intolerance to anti-TB first-line drugs and interaction with the antiretroviral drugs used in the treatment of HIV were the most frequent indications for the use of FQ in the group of pa-

tients under study in a general hospital. Although we agree with most studies on the low probability of adverse events and the good hepatic safety profile associated with these drugs in extended treatments, the absence of adverse events in our study may be related to the low number and younger age of the patients included.

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