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DRUGS
Narrative review

Role of fluoroquinolones in the treatment of tuberculosis

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Abstract

Introduction: The increasing incidence of multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Mycobacterium tuberculosis* is hampering efforts to control the global tuberculosis (TB) epidemic. Although treatment of drug-susceptible TB is possible in ≥ 95% of disease cases, long (≥ 6 months) duration of supervised combination therapy is challenging. Non-adherence to treatment often results in much lower cure rates. Treatment of MDR-TB and XDR-TB is far less effective. The aim of this review is to summarize the current status of fluoroquinolones in shortening the duration of drug-susceptible pulmonary TB and in improving the outcome of MDR-TB/XDR-TB.

Methods: All the relevant articles were identified through a search of PubMed and Scopus databases by using search terms like tuberculosis (or *M. tuberculosis*), fluoroquinolones, drug-susceptible TB, MDR-TB, XDR-TB, combination therapy, treatment regimens, treatment duration, drug target and drug resistance. The current literature on the role of fluoroquinolones in the treatment of TB was reviewed.

Results: The fluoroquinolones, particularly newer compounds such as levofloxacin, moxifloxacin and gatifloxacin, have bactericidal activity against *M. tuberculosis*, excellent oral bioavailability, favorable safety profile and no cross-resistance with other first-line anti-TB drugs. Data from phase II trials of fluoroquinolones-containing regimens for shortening the duration of treatment for pulmonary TB are encouraging and phase III trials are currently underway. The fluoroquinolones are also effective as substitute agents for those individuals who are intolerant to first-line drugs. Several studies and clinical trials have also supported the use of fluoroquinolones in patients with MDR-TB/XDR-TB.

Discussion: The fluoroquinolones-containing regimens are being tested to shorten the duration of treatment for pulmonary TB to 4 months. They are also regarded as one of the two cornerstone drugs for the treatment of MDR-TB/XDR-TB. However, they are also among the commonly prescribed antibiotics for lower respiratory tract infections and are becoming increasingly associated with delayed treatment and resistance in TB. If these trends are not reversed soon, we may lose fluoroquinolones as effective anti-TB agents very rapidly.

Keywords

Fluoroquinolones; Drug-susceptible tuberculosis; Multidrug-resistant tuberculosis; Resistance

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Introduction

Despite concerted worldwide efforts, tuberculosis (TB) continues to remain a major public health issue of our times as it contributes considerably to illness and death around the world. Active TB disease is caused primarily by the obligate human pathogen *Mycobacterium tuberculosis*. Currently, the TB epidemic is being sustained and fuelled by two major factors: global human immunodeficiency virus (HIV) infection and its association with active TB disease and increasing resistance of *M. tuberculosis* strains to the most effective (first-line) anti-TB drugs [1,2]. Other factors contributing to the resurgence of active TB disease include inadequate TB control and prevention programs as well as poor case detection/cure rates in endemic countries, and disease association with other underlying conditions including diabetes [1-3].

Close contact with sputum-positive pulmonary TB patients is mainly responsible for new infections in a community. Incidentally, primary infection with *M. tuberculosis* leads to clinical disease in only ~10% of exposed individuals while initial growth and multiplication of *M. tuberculosis* is arrested by the protective immune response in the remaining cases. However, pathogen clearance occurs in ~10% people while the remaining ~90% individuals succeed in containment of infection only as some bacilli escape killing and remain in non-replicating (latent) state in granulomatous lesions [4]. The dormant bacilli can resuscitate and cause active TB in the event of disruption of host's immune response [5]. The World Health Organization (WHO) has estimated that 2.2 billion people worldwide are now latently infected with *M. tuberculosis* and 5-10% of the infected individuals will eventually develop active TB disease during their life time [5,6]. However, the annual risk of active TB is 5-15% and the lifetime risk is ~50% in HIV-seropositive individuals [1,7].

Epidemiology of TB and drug-resistant TB

The current estimates of global burden of TB are based on the results of yearly surveys conducted by the WHO for the prevalence of infection. In 2009, 9.4 million incident cases of active TB disease and 1.68 million deaths occurred worldwide [1]. Most of the estimated TB cases in 2009 occurred in Asia (55%) followed by Africa (30%) while smaller proportions of cases occurred in Eastern Mediterranean region (7%), European region (4%) and the region of the Americas (3%). The highest incidence rate (340 per 100,000 population) was recorded for the African region, mainly due to higher prevalence of concomitant HIV infection [1]. Pulmonary TB accounted for > 85% of active TB cases in high TB incidence countries while extrapulmonary TB was more common in low TB incidence countries [1,8,9]. The WHO has also performed surveys for estimating drug susceptibility testing (DST) data for first-line drugs: isoniazid (INH), rifampicin (RMP), ethambutol (EMB) and streptomycin (SM) [2]. Resistance to at least one anti-TB drug (defined as "any resistance") among previously treated TB patients (25.1%) was higher than in new TB cases (11.1%). The worldwide average for multidrug-resistance (MDR) (defined as infection with *M. tuberculosis* strains resistant at least to INH and RMP) was also higher in previously treated TB cases compared to new cases (11.7% versus 1.6%, respectively). Monoresistance to RMP occurs rarely except in individuals co-infected with HIV or with other underlying conditions and resistance to RMP is considered a good surrogate marker for infection with MDR strains of *M. tuberculosis* (MDR-TB) [2,10,11]. The highest percentage of MDR-TB cases have been estimated for Eastern European countries (19.2%) followed by Western Pacific region (7%) and Southeast Asia (4.3%). Overall, ~440,000 cases of MDR-TB occurred in 2008, resulting in 150,000 deaths [12].

The MDR-TB is a major threat to global public health as it is more difficult to treat than drug-susceptible TB and often results in relapse or treatment failure [13-16]. It is also a risk factor for the emergence of extensively drug-resistant (XDR) TB (defined as infection with MDR-TB strains additionally resist-

ant to a fluoroquinolone and an injectable anti-TB agent such as kanamycin, amikacin, capreomycin or viomycin) [12,17]. The XDR-TB is more difficult to treat than MDR-TB even in developed countries and is virtually an untreatable disease in much of the developing world [18-22]. By 2009, the presence of XDR-TB has been documented in 58 countries. Nearly 5.4% of all MDR-TB cases were found to have XDR-TB in 46 countries while eight countries reported XDR-TB in > 10% of all MDR-TB cases. No information on the incidence of XDR-TB is available for several other countries that have a high incidence of MDR-TB and many of these countries have reported a high incidence of fluoroquinolone resistance among MDR-TB strains, indicating that the worldwide incidence of XDR-TB is likely to climb further [12].

Fluoroquinolones as anti-TB drugs

Fluoroquinolones (FQs) are broad-spectrum bactericidal antimicrobial agents that are currently being used for a variety of bacterial infections including respiratory infections other than TB [23-27]. The older FQs, such as ciprofloxacin (CFX) and ofloxacin (OFX), are synthetic derivatives of nalidixic acid and are highly effective as antibacterial agents. New generation FQs such as levofloxacin (LFX), two 8-methoxy-fluoroquinolones (mFQs), moxifloxacin (MFX) and gatifloxacin (GFX), are more potent antibacterial agents. These drugs are a relatively recent addition to the armamentarium against *M. tuberculosis* [28-31]. The minimum inhibitory concentration (MIC), recommended daily oral dose, early bactericidal activity (EBA, a measure of reduction in viable colony forming units during the first few days of therapy), pharmacokinetic and other properties of different FQs are summarized in Table I. Higher daily oral doses of CFX (1500 mg), OFX (800 mg) and LFX (1000 mg) have also been used safely in TB patients with normal renal functions [28,30]. The MIC values for mFQs (MFX and GFX) are lower than for other FQs and are comparable to the range of MIC values of first-line anti-TB drugs:

Anti-tubercular drug	Chemical nature	MIC range (mg/l)	Oral daily dose (mg)	Peak serum concentration (mg/l)	Early bactericidal activity (0-2 days) at oral dose (mg)	CSF penetration (% of serum level)	Drug-related major side-effects
Ciprofloxacin, CFX	Fluoroquinolone	0.25-2.0	750	1.5-4.0	0.21/1500	Poor (10-20%)	GI/CNS disturbances
Ofloxacin, OFX	Fluoroquinolone	0.25-2.0	600	2.5-4.0	0.32-0.38/800	Fair (20-40%)	GI/CNS disturbances
Levofloxacin, LFX	Fluoroquinolone	0.25-2.0	750	8.0-12.0	0.45/1000	Good (40-60%)	GI/CNS disturbances
Moxifloxacin, MFX	8-methoxy-fluoroquinolone	0.125-0.5	400	3.0-4.0	0.33-0.53/400	Excellent (> 60%)	GI/CNS disturbances, arrhythmias
Gatifloxacin, GFX	8-methoxy-fluoroquinolone	0.062-0.5	400	0.75-2.0	0.35/400	Good (40-50%)	GI/CNS disturbances, dysglycemia

Table I. The minimum inhibitory concentration (MIC), recommended oral daily dose, bactericidal and pharmacokinetic properties and major drug-related side effects of various fluoroquinolones in the treatment of tuberculosis

GI/CNS disturbances = signs and symptoms of disturbance of the gastrointestinal system or central nervous system

- INH = 0.02-0.04 mg/l;
- RMP = 0.2-0.4 mg/l;
- EMB = 0.5-2.0 mg/l;
- SM = 0.5-2.0 mg/l.

The EBA (0-2 days) of MFX and GFX and high dose LFX (and to a lesser extent high dose OFX) is close to or equal to that of INH (recorded as 0.5-0.6 at oral dose of 300 mg), which is regarded as the most effective anti-TB drug in the intensive phase of chemotherapy [32-36]. The CFX is the least effective FQ against *M. tuberculosis* as the EBA of even high dose CFX is quite low (Table I). Thus, high dose LFX and normal dose GFX and MFX are bactericidal while even high dose CFX is bacteriostatic for *M. tuberculosis*.

The potent EBA of MFX and GFX, against *M. tuberculosis* and once daily oral dosing make these drugs highly desirable agents for combination therapy of fully susceptible pulmonary TB (Table II) [34-39]. Since RMP was inducted in combination therapy more than forty years ago, these drugs are the first new antibiotic class to be considered as first-line agents against active TB disease and are currently being evaluated for shortening the treatment duration of fully susceptible pulmonary TB. The FQs (MFX and GFX as well as high dose OFX and LFX) with the exception of CFX are also useful as second-line agents for the treatment of TB patients who are intolerant to some of the first-line drugs as well as for the treatment of drug-resistant TB [30,31,37]. Although early studies used OFX for the treatment of drug-resistant TB and MDR-TB, more recent studies in developed countries have mainly used high dose LFX (even though it is more expensive than OFX), due to bactericidal and better pharmacokinetic properties, in therapy regimens for the treatment of MDR-TB patients [30-32,37]. However, due to lower cost, OFX is still being used for the treatment of MDR-TB patients in developing countries.

Early studies carried out in murine models of TB suggested that replacement of EMB or INH with MFX in first-line treatment for TB has the potential to improve outcome and to shorten therapy to four months from the current standard of six months [40,41]. The maximum treatment benefit was noted when MFX was used in place of INH in the murine model of TB [40]. The effect of replacement of EMB with standard dose of MFX or GFX (each at 400 mg) was evaluated in three separate phase II clinical trials in the intensive phase of treatment of sputum smear-positive pulmonary TB patients which yielded variable results. The first of these studies, carried out by the TB Trials Consortium, reported higher rates of sputum culture conversion at 4 and 6 weeks of therapy but not at week 8 in MFX-containing regimen [42]. Another study conducted in Rio de Janeiro, Brazil, also reported higher rates of sputum culture conversion beginning at 2 weeks and persisting till week 8 of therapy in MFX-containing regimen [43]. The third study carried out in Durban, South Africa (OFLUTUB Consortium study) also evaluated the replacement of EMB by MFX or GFX (or by OFX at 800 mg) in the intensive phase of standard WHO recommended 6-month regimen. This study reported rapid elimination of

Fluoroquinolone drug	Recommended for TB disease status*	Intended aim	Current stage in clinical practice
Ciprofloxacin, CFX	Not recommended	None	Not in use
Ofloxacin, OFX	MDR-TB	Treatment	Phase II
Levofloxacin, LFX	MDR-TB	Treatment	Phase II
Gatifloxacin, GFX	FS-PTB	Shortening duration	Phase III
Moxifloxacin, MFX	FS-PTB	Shortening duration	Phase III

Table II. The current status of various fluoroquinolones in the treatment of tuberculosis patients suffering from various forms of the disease

FS-PTB = fully susceptible pulmonary tuberculosis; MDR-TB = multidrug-resistant tuberculosis

viable bacteria from sputum of pulmonary TB patients when MFX or GFX was substituted for EMB while no measurable improvement was noted when EMB was replaced by OFX [44].

The effect of replacement of INH with MFX was also evaluated in a phase II double blind, randomized controlled trial in the intensive phase of treatment of sputum smear-positive pulmonary TB patients. The conversion from positive sputum cultures at initiation of therapy to negative cultures from sputum specimens after 8 weeks of therapy occurred in 99 (60.4%) of 164 participants in MFX group versus 90 (54.9%) of 164 participants in the INH group. The data showed a slight but statistically insignificant ($p = 0.37$) increase in sputum conversion rate in MFX-containing regimen [45]. The FQs (particularly older FQs) have generally been regarded as relatively safer drugs that are well tolerated by most individuals [27,30,46]. During clinical trials of TB patients, nearly similar number of adverse drug events (AEDs) have been recorded in the FQ arm compared to the control arms [30,32]. In the clinical trial involving replacement of INH with MFX, serious adverse events were recorded in 9 of 214 TB patients in the MFX arm compared to 8 of 205 TB patients in the control arm. Serious adverse events related to therapy were recorded in 3 TB patients in the MFX arm and in 2 TB patients in the control arm [45]. Thus, unlike some FQs (such as grepafloxacin and sparfloxacin) which were withdrawn from the market due to QTc interval prolongation, the recommended daily dose (400 mg) of MFX appears to be safe in most TB patients. However, FQs (including MFX and GFX) are known to produce cardiac QTc interval prolongation in some patients which limits the recommended daily dose (400 mg) of these two compounds that can be safely administered during anti-TB treatment [47]. Furthermore, GFX is contraindicated in some TB patients as it can cause dysglycemic events, which seem to occur more frequently in elderly and/or diabetic subjects [48].

The results of the four phase II trials involving MFX and GFX have shown that replacement of either MFX or GFX with EMB or replacement of MFX with INH is at least as efficacious as the standard intensive phase of therapy and may even contribute towards more rapid clearing of the infected lungs by rapidly dividing tubercle bacilli [42-45]. Both mFQs are now in two separate phase III clinical trials for the treatment of adult patients newly diagnosed with drug sensitive, pulmonary TB for investigation of whether treatment duration can be effectively shortened to 4 months by substitution of GFX for EMB or MFX for either EMB or INH [49,50]. The results of these trials will be compared with the WHO therapy regimen of 6 months duration with four standard first-line drugs. The advantages of an efficacious four-month treatment regimen are obvious. They will greatly reduce the economic burden of delivering TB treatment in impoverished countries and improve treatment-completion rates. The evolution and spreading of drug resistant and MDR strains of *M. tuberculosis* will also be reduced considerably.

The FQs, particularly new generation FQs such as LFX, MFX and GFX due to their potent bactericidal activity and lack of cross-resistance with existing anti-TB drugs, have also been used extensively for the treatment of drug-resistant TB and are now regarded as one of the two most important second-line agents for the treatment of MDR-TB [22,28,31,36,51,52]. Several studies have shown that inclusion of a FQ (particularly mFQs) and an injectable aminoglycoside (kanamycin or amikacin) or cyclic peptide (capreomycin and viomycin) in multidrug treatment regimens has the maximum effect for a more favorable outcome in the treatment of MDR-TB [12-14,51-54]. This is also apparent from the fact that development of resistance of MDR-TB strains to FQs is associated with poor treatment outcome. Additional development of resistance of MDR-TB strains to FQs is also one of two key defining conditions of XDR-TB [12-14,53-55]. Although initial studies were carried out with OFX-containing regimens, some studies and clinical trials involving MDR-TB patients in developed countries have also used LFX in treatment regimens. This is due to the fact that high dose LFX is bactericidal while OFX is bacteriostatic. More recently, MFX which is also bactericidal at the daily recommended oral dose, has also been used for the treatment of MDR-TB patients. A phase III clinical trial to compare the effectiveness of LFX and MFX on the culture conversion after three months of treatment among MDR-TB patients

is currently underway [56]. However, OFX continues to be used for the treatment of MDR-TB patients due to its lower cost compared to the other two FQs.

The FQs have also been useful for the treatment of central nervous system infections as favorable drug concentrations were achieved in cerebrospinal fluid (CSF) at daily recommended dose (for GFX and MFX) or high-dose (for LFX) administration of these agents in several studies [57-59]. Thus, addition of a FQ early in the course of therapy is likely to improve outcome in the treatment of tuberculous meningitis, particularly when MDR-TB is suspected or confirmed [60,61]. A phase II clinical trial is currently underway to evaluate the pharmacokinetics, pharmacodynamics and tolerability of MFX in intensive treatment regimens for TB meningitis [62]. The current clinical development status of important FQs in the treatment of drug-susceptible pulmonary TB and MDR-TB is summarized in Table II. While more potent FQs (MFX and GFX) are being evaluated for shortening the duration of treatment of fully susceptible pulmonary TB, OFX and LFX are being used mainly for the treatment of MDR-TB patients. Although FQs, particularly new generation mFQs like MFX and GFX, have the potential to contribute to chemotherapy of TB, resistance of *M. tuberculosis* strains to FQs has also been detected in nearly all the countries of the world that are endemic for TB [12].

Mechanism of action and resistance of fluoroquinolones in *M. tuberculosis*

Resistance of *M. tuberculosis* to anti-TB (both, first-line and second-line) drugs is caused exclusively by chromosomal mutations occurring at a predictable rate in genes encoding drug targets that reduce the susceptibility of *M. tuberculosis* to specific anti-TB drugs [16,63]. Thus, mutations in target genes, *rpoB, katG, inhA, embB, rpsL, rrs* and *pncA* are the major mechanisms conferring resistance of clinical *M. tuberculosis* strains to first-line anti-TB drugs RMP, INH, INH, EMB, SM, SM and PZA, respectively [16,64-79]. The cellular target of FQs in *M. tuberculosis* is DNA gyrase, a type II topoisomerase that controls negative supercoiling in bacterial DNA. Only one type II topoisomerase activity is present in *M. tuberculosis*, which is also the main target for FQ activity in this organism. The active enzyme is a tetramer, consisting of two A and two B subunits that are encoded by *gyrA* and *gyrB* genes, respectively. Studies have shown that inhibition of DNA gyrase activity by FQs results in inhibition of DNA replication, transcription and repair, causing cell death [37,80-82]. Clinical *M. tuberculosis* isolates with wild-type *gyrA* and *gyrB* gene sequences are highly susceptible to FQs while chromosomal mutations in clinical *M. tuberculosis* strains in *gyrA* and *gyrB* genes usually confer moderate to high-level resistance to FQs [37,65,83-85]. In some *M. tuberculosis* strains, changes in the drug efflux pump systems may also result in low-level resistance to FQs [86].

Early *in vitro* studies, performed with laboratory strains of virulent *M. tuberculosis* and *Mycobacterium smegmatis* (a non-pathogenic species) showed that resistance to FQs results from missense mutations causing amino acid alterations in the conserved and putative FQ binding region in *gyrA* or *gyrB* genes [85,87]. The presence of missense mutations in the so-called quinolone resistance-determining region (QRDR) of *gyrA* or *gyrB* genes conferring resistance to FQs was subsequently confirmed by using clinical *M. tuberculosis* isolates in multiple studies [83-85,87-97]. The presence of S95 or T95 at *gyrA* codon 95 is a naturally occurring polymorphism that is not associated with resistance of *M. tuberculosis* isolates to FQs. However, this polymorphism together with *katG* codon 463 polymorphism (R463 or L463), is used to define the three principal genetic groups of worldwide collection of *M. tuberculosis* strains [98-100]. The FQ-resistant clinical *M. tuberculosis* isolates more frequently contain mutations in *gyrA* gene, particularly at codon 90 (A90) or codon 94 (D94) but also occasionally at codon 74 (A74), codon 88 (G88) and codon 91 (S91) while mutations in few codons of the *gyrB* gene occur in a small minority of clinical strains [83,89-91]. Surprisingly, some *M. tuberculosis* isolates have also been

described that are hypersusceptible to FQs due to mutations at *gyrA* codon 80 (T80), particularly in association with other FQ resistance-associated mutations [83]. Recent studies have shown that the vast majority (~90%) of FQ-resistant *M. tuberculosis* strains can be accurately detected by analysis of QRDR of *gyrA* gene alone since additional targeting of *gyrB* gene did not enhance the sensitivity significantly [91,93-95]. Attempts have also been made to correlate the nature and kind of *gyrA* mutations with the level of resistance to FQs in *M. tuberculosis* strains with conflicting results. Some studies have reported that *M. tuberculosis* strains containing D94G mutation in the *gyrA* gene exhibit high-level resistance to FQs while those with D94A mutation have lower MIC for LFX [93,96,97]. On the contrary, other reports have not found an association of different mutation patterns in *gyrA* or *gyrB* genes with the level of FQ resistance in *M. tuberculosis* isolates [89,94].

Several genotypic tests have recently been developed (Table III) for rapid (within 1-2 days) detection of vast majority of FQ-resistant clinical *M. tuberculosis* isolates [95]. Although some of these assays target both *gyrA* and *gyrB* genes, the majority of genotypic tests target only QRDR of *gyrA* gene for simplicity and acceptable levels of sensitivity. The genotypic tests that have been developed include PCR-DNA sequencing [83-85], PCR-single strand conformation polymorphism [101], temperature-mediated heteroduplex analysis by using denaturing high-pressure liquid chromatography (HPLC) [102], pyrosequencing [103], microchip array [104], locked nucleic acid probe real-time PCR [105], multiplex PCR amplimer conformation analysis [89] and both, in-house developed as well as commercially available line probe assays [92,96,97].

The FQs are an important component of the therapy regimens for patients with MDR-TB or XDR-TB since their inclusion greatly improves treatment outcome. Furthermore, resistance of MDR-TB or XDR-TB strains to FQs has been shown to increase the risk of treatment failure and death [15,18,53,55,106]. Although all FQs share the same drug targets (*gyrA* and *gyrB*) and cross-resistance between different FQs is generally assumed, there are some reports contrary to these generalizations. A study from Hong Kong showed that LFX was effective against some OFX-resistant *M. tuberculosis* strains [107]. Furthermore, one *M. tuberculosis* strain resistant to both MFX and GFX with mutation at *gyrB* codon 533 (N533T) has also been isolated recently that exhibited *in vitro* susceptibility to OFX [91]. These findings suggest that cross-resistance between different FQs is not always complete. Nonetheless, resistance of *M. tuberculosis* strains to FQs, including third-generation compounds (MFX and GFX), has been described from several countries worldwide [2,12,84]. Recent WHO reports suggest that nearly 25% of MDR-TB strains from China and India, the two countries accounting for nearly 35% of all estimated

Genotypic method	Target gene(s)	Turn around time (days)	% of FQ-resistant strains detected	Selected reference(s)
PCR-DNA sequencing	*gyrA* + *gyrB*	1-2	43-96	86,96-98
HDA by d-HPLC	*gyrA*	1-2	100	103
Pyrosequencing	*gyrA*	1-2	70	104
Microchip array	*gyrA*	1	92	105
LNAP-rtPCR	*gyrA*	1	71	106
mPCR-ACA	*gyrA*	1-2	58	192
Line probe assays	*gyrA*	1-2	89-100	95,99,100

Table III. Performance of various genotypic methods for rapid detection of fluoroquinolone-resistant strains of *M. tuberculosis*

d-HPLC = denaturing high-pressure liquid chromatography; HDA = heteroduplex analysis; LNAP-rtPCR, = locked nucleic acid probe-real-time PCR; mPCR-ACA = multiplex PCR-amplimer conformation analysis; SSCP = single strand conformation polymorphism

active TB disease cases and 50% of estimated MDR-TB cases worldwide, are likely to be resistant to FQs [1,12]. Several other high TB incidence countries are also predicted to have a high prevalence of FQ resistance among MDR-TB strains [12]. Furthermore, the incidence of resistance of *M. tuberculosis* strains to FQs also appears to be increasing in several developing countries [108-111].

How we are creating FQ-resistant TB

The history of treatment of active TB disease during early days of chemotherapy has shown that resistance to anti-TB drugs develops soon after they are introduced into therapy regimens. This is exemplified by development of resistance of *M. tuberculosis* to SM which developed soon after the drug was used as monotherapy in the 1940s [112]. Although para-aminosalicylic acid (PAS) and INH were subsequently introduced into combination therapy to suppress the development of resistance to SM, resistance to both SM and INH soon became widespread and a challenge to combination therapy. It was only when RMP and pyrazinamide (PZA) were introduced into combination therapy and the duration was reduced to six months that the problem of drug resistance was brought under control [113,114]. However, widespread use and misuse (due to poor quality of medications, non-adherence of TB patients to treatment, etc.) of short-course regimens have also resulted in the emergence and spreading of MDR-TB strains in the 1980s.

Today, a major impediment in the effective use of FQs in the treatment of both drug-susceptible TB and MDR-TB is rapidly emerging due to pre-existing and/or increasing levels of FQ resistance among *M. tuberculosis* strains in several countries. Although FQ-resistant TB is mainly generated by the use of these drugs in anti-TB treatment regimens, these agents are also being used widely in the treatment of other infections including acute lower respiratory tract infections. This is further complicated by easy, uncontrolled access of these drugs in many developing countries. Furthermore, the published expert recommendations and clinical guidelines in some countries have promoted widespread use of FQs for common infections such as pneumonia and sinusitis. For example, the consensus guidelines of the Infectious Disease Society of America (IDSA)/American Thoracic Society (ATS) have recommended empiric therapy with a FQ for the management of community-acquired pneumonia as a first-line selection in several clinical situations, including those with comorbid conditions like renal disease, diabetes or immunosuppression [115]. Incidentally, most of these conditions also increase the risk of developing active TB disease in an individual. Thus, such clinical practices are likely to contribute to the emergence of FQ resistance in *M. tuberculosis*. The same conclusions were also advocated by a recent study from the United States. This study showed that the risk of FQ-resistant TB was higher in patients who had received FQs for more than 10 days for lower respiratory tract infections, particularly if the drug was prescribed 60 days or earlier but before the diagnosis of active TB disease [116]. A more recent systematic review and meta-analysis has also shown that empirical treatment of pneumonia with FQs was associated with longer delays in diagnosis and treatment of pulmonary TB and a higher risk of developing FQ-resistant TB [117]. The empirical FQ prescriptions are certainly

Questions for further research

The effectiveness of FQs in the treatment of various forms of TB needs further evaluation and validation. Two phase III clinical trials are currently underway to evaluate the effectiveness of a 4-month therapy regimen for the treatment of pulmonary TB involving substitution of GFX for EMB or MFX for either EMB or INH. A phase III trial to compare the effectiveness of LFX and MFX on the culture conversion after three months of treatment among MDR-TB patients is also being carried out presently. A phase II clinical trial to evaluate MFX in treatment regimens for TB meningitis is also currently underway.

more problematic in developing countries with a high TB incidence since patients diagnosed with lower respiratory tract infections in such settings may, in fact, have a much higher chance of active TB disease than in low TB incidence developed countries and the diagnosis of their active disease may be substantially delayed by monotherapy with FQs. Thus, if we plan to protect FQs for the treatment of TB, great caution is warranted while considering the use of FQs in the community setting and to limit/avoid the use of prolonged or repeated courses of FQs in patients who may be at higher risk of having active TB disease.

The review in brief	
Clinical question	Role of fluoroquinolones in the treatment of tuberculosis
Type of review	Narrative review
Search of the literature	Relevant articles from PubMed and Scopus, with keywords: tuberculosis (or *M. tuberculosis*), fluoroquinolones, drug-susceptible TB, MDR-TB, XDR-TB, combination therapy, treatment regimens, treatment duration, drug target and drug resistance
Conclusions	The FQ-containing regimens are being tested to shorten the duration of treatment for pulmonary TB to 4 months. They are also regarded as one of the two cornerstone drugs for the treatment of MDR-TB
Limitations	The FQs are among the most commonly prescribed antibiotics for lower respiratory tract infections and are becoming increasingly associated with delayed treatment and resistance in TB. If these trends are not reversed soon, we may lose FQs very rapidly

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