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MINIREVIEW

Current Prospects for the Fluoroquinolones as First-Line Tuberculosis Therapy▽

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While fluoroquinolones (FQs) have been successful in helping cure multidrug-resistant tuberculosis (MDR TB), studies in mice have suggested that if used as first-line agents they might reduce the duration of therapy required to cure drug-sensitive TB. The results of phase II trials with FQs as first-line agents have been mixed, but in at least three studies where moxifloxacin substituted for ethambutol, there was an increase in the early percentage of sputa that converted to negative for bacilli. Phase III trials are in progress to test the effectiveness of 4-month FQ-containing regimens, but there is concern that the widespread use of FQs for other infections could engender a high prevalence of FQ-resistant TB. However, several studies suggest that despite wide FQ use, the prevalence of FQ-resistant TB is low, and the majority of the resistance is low-level. The principal risk for resistance may be when FQs are used to treat nonspecific respiratory symptoms that are in fact TB, so curtailing this use of FQs could reduce the development of resistance and also the delays in TB diagnosis and treatment that have been documented when an FQ is given in this setting. While the future of FQs as first-line therapy will likely depend upon the results of the ongoing phase III trials, if they are to be effectively employed in high-TB-burden regions their use for community-acquired pneumonias should be restricted, the prevalence of FQ-resistant TB should be monitored, and the cost of the treatment should be comparable to that of current standard drug regimens.

There are two main problems with tuberculosis (TB) chemotherapy, and the fluoroquinolones (FQs) may be able to help with both. First, although the total duration of treatment has been reduced from 18 to 24 months to 6 months by the systematic use of rifampin (RIF) and pyrazinamide, such a 6-month duration is still very long for patients and burdensome for health services in numerous countries where TB is highly endemic and can lead to the second problem, the development of strains resistant to the drugs. The success of the fluoroquinolone antibiotics in treating strains that are resistant to the standard first-line drugs has led to the suggestion that if used as first-line therapy they may be able shorten the duration of treatment. However, excitement over this possibility is tempered by the fear that their widespread community use for other infections will engender a high prevalence of FQ-resistant TB strains in the population.

FQs: HIGH HOPES BUT ALSO HIGH RATES OF RESISTANCE

The quinolones are synthetic molecules that got their start when nalidixic acid was discovered in 1962 (47) and then introduced into clinical use in 1967 for the treatment of Gram-negative urinary tract infections (26). The addition of a fluorine atom significantly increased their antibacterial activity, and by adding various side groups literally thousands of different fluoroquinolones were synthesized. Although the increased broad-spectrum activity of ciprofloxacin (CIP) created the expectation that it would be a valuable agent against troublesome bacteria such as *Staphylococcus aureus*, resistance in these bacteria developed rapidly. Within just a few years after the introduction of CIP, many nosocomial strains (9) were resistant (10), especially Gram-positive bacteria. In contrast, CIP has remained effective much longer against some enteric Gram-negative bacteria, such as *Escherichia coli* (49). The difference appeared to be related to the ratio of the usual serum drug concentration to the innate MIC of the bacteria. The MICs for CIP of many Gram-positive bacteria, such as *S. aureus*, are $\geq$0.25 μg/ml, about four times higher than the MIC for *E. coli.* Studies *in vitro* have shown that as the FQ concentration increases, the frequency at which FQ-resistant colonies appear decreases, eventually reaching a "mutant prevention concentration" (MPC) well above the MIC, at which resistant colonies are quite rare ($<$1 in 10^9 to 10^{10} bacteria) (5, 23).

FQs PLAY AN IMPORTANT ROLE IN THE TREATMENT OF MDR TB

When multidrug-resistant (MDR) TB (tuberculosis resistant to at least isoniazid [INH] and RIF) appeared in the early 1990s, clinicians reached for the popular fluoroquinolone at the time, CIP (75). Resistant strains appeared rapidly, which could have been predicted from *in vitro* studies showing that resistant colonies can be isolated at relatively high frequencies ($\sim 10^{-7}$) (78) at the usual serum concentration of ~2 μg/ml, which is only about 2× the MIC for *Mycobacterium tuberculosis*. However, CIP was worse than just ineffective (6), because

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while it contributed little to curing TB (71), it selected for strains that were also resistant to other, more active, FQs (35).

When treatment of MDR TB began to include the newer FQs ofloxacin (OFX) and its L-isomer, levofloxacin (LVX), the only active part of this racemate, they were shown to be a significant factor in curing patients (14, 61, 76, 94). The better efficacy of these drugs over CIP appears to be somewhat complex, involving higher MPCs, better pharmacokinetics, and better intramacrophage penetration (71). There are other FQs with lower MICs for tuberculosis, often with a methoxy group at the C_8 position (66), but some of the most active were found to be too toxic for widespread use: sitafloxacin and sparfloxacin are phototoxic (19), and the promising FQ gatifloxacin (GAT) caused problems with hypoglycemia and hyperglycemia, especially in older patients (93). That left moxifloxacin (MOX) as the best hope for an expanded FQ role in treatment of TB (29), although clinical trials are still ongoing with GAT (38) (see Table 2).

FQs AS FIRST-LINE ANTI-TB AGENTS: CAN THEY REDUCE THE DURATION OF THERAPY?

The effectiveness of the FQs *in vitro* (69), their early sterilizing effect in mice and humans (44, 63), and their success in treating MDR TB all raised the hope that as first-line drugs they might be able to reduce the duration of therapy. This would cut down the number of required clinic visits and the burden on the health care system and could also decrease the percentage of patients who fail to complete the full course of treatment and are therefore more likely to relapse and develop drug resistance. Previous attempts to reduce the duration of therapy to 4 months using the standard drugs resulted in unacceptably high rates of relapse (24, 72).

Studies with a mouse model of TB tested whether it is possible to reduce the duration of therapy for pan-sensitive TB by incorporating MOX into a first-line regimen. When MOX was added to the standard treatment scheme of 2 months of rifampin, isoniazid, ethambutol (EMB), and pyrazinamide followed by 4 months of rifampin and isoniazid, there was no improvement in the time it took to eliminate viable bacilli from the lung and spleen. When MOX was substituted for either rifampin or pyrazinamide, the results were worse. When MOX substituted for isoniazid though, cultures from the lung and spleen converted to negative a month earlier than with the standard drug regimen (57). A subsequent study compared 2 months of rifampin, isoniazid, and pyrazinamide followed by 4 months of rifampin and isoniazid to the same regimen but with MOX in place of isoniazid. With the isoniazid regimen, the full 6 months of treatment was required to cure mice infected with *M. tuberculosis*, but with MOX and rifampin, lasting cure could be achieved after only 4 months, with the addition of pyrazinamide required only for the first month (58).

There have been several clinical trials to see if FQs would be similarly effective against human TB (Table 1). Initial studies substituting OFX for ethambutol (45) or simply adding LVX to the standard regimen (25) did not improve results, but recent studies have used the more active agent, MOX. A study adding MOX to the conventional TB drug regimen (90) found an increase in sputum conversion to negative at 6 but not at 8 weeks and an overall shorter medium time to sputum conversion. Based on the success in the mouse model, a trial substituted MOX for isoniazid, but this achieved only a small, statistically nonsignificant increase in sputum conversions at 8 weeks (22). There were, however, problems in the design and execution of this multicenter study, so it may not have provided an adequate assessment.

Studies substituting MOX for ethambutol have been more encouraging (Table 1). One study found that MOX improved sputum conversion at 4 and 6 weeks, but there was no difference at 8 weeks. This study also found that dosing 5 times a week instead of 3 produced only a slight, nonsignificant improvement in sputum conversions at 8 weeks (12). The phase II OFLOTUB trial tested three FQs against ethambutol and found that MOX was slightly better than GAT in the speed of sputum conversion, and both were better than OFX, which was equivalent to ethambutol (70). At 8 weeks, though, there were no significant differences in the percentages of sputum conversion. It was also noted that more sputa are found to be negative when cultured on solid media than in liquid media.

These two studies showed that MOX is superior to ethambutol at early bacterial killing, and a subsequent study found that MOX was also significantly better than ethambutol at achieving sputum conversion to negative at the critical 8-week mark (17). Because sputum conversion at 8 weeks is regarded as indicating the likelihood of cure after completion of therapy (55, 68), these results were proposed as evidence that MOX has the potential to reduce the duration of first-line TB therapy. In the 1970s, the introduction of rifampin led to a 15 to 20% increase in sputum conversion at 8 weeks and allowed the duration of therapy to be reduced from 18 months to 9 months. The later introduction of pyrazinamide caused a further 13% increase in sputum conversion at 8 weeks, allowing therapy to be reduced from 9 months to 6 months.

Although sputum conversion at 8 weeks is not universally accepted as a reliable indicator of cure after completing therapy, there isn't a more accurate predictive biomarker currently available (59). The only true indicator of effectiveness at present is the absence of recurrence in the months or years after completion of therapy. Although most recurrences will likely occur in the first 6 months, monitoring through at least 2 years after completing treatment is prudent.

These published clinical trials only administered MOX during the 2-month intensive phase of treatment and used sputum conversions as an indicator of its capacity to rapidly kill bacilli and thus its potential to shorten the total duration of required therapy. Based on these studies, three trials (Table 1) are currently in progress to test whether 4 months of an FQ-containing regimen will be as effective as 6 months of the standard regimen: phase III of the REMox study (http://www.clinicaltrials.gov/ct2/show/NCT00864383?term=tuberculosis+moxifloxacin&rank=3), the RIFAQUIN study (8), and phase III of the OFLOTUB study (http://www.sgul.ac.uk/depts/medmicro/. . ./OflotubTrialMitchisonLondon07.pdf).

WILL WIDESPREAD COMMUNITY USE OF FQs LIMIT THEIR EFFECTIVENESS AGAINST TB?

Even if MOX can be shown to effectively shorten the duration of first-line therapy, the threat of resistance is a reason for caution: the history of FQ use against other resistance-prone

TABLE 1. Clinical trials of FQs as first-line agents

Study (reference)	Site	Comparison(s)	Exptl regimen(s)[a]	Result(s)[b]
Kohno et al. (45)	Nagasaki, Japan	OFX vs EMB daily for 9 mo, with OFX at 0.6 g/day for 2 mo and then 0.3 g/day for 7 mo	9EHR, 9OHR	No significant differences; OFX = EMB
el-Sadr et al. (25)	United States	Pulmonary TB in HIV^+ patients; LVX added to 4-drug standard regimen given daily for 2 wk and then 3 times/wk, followed by 18 or 31 wk of RIF-INH 2 times/wk	2EHRZ 3 times/wk/4RH 2 times/wk, 2EHRZ 3 times/wk/7RH 2 times/wk, 2EHRZL 3 times/wk/4RH 2 times/wk, 2EHRZL 3 times/wk/7RH 2 times/wk	No added benefit with addition of LVX (small increase in sputum conversion at 2 wk); no differences 6- or 9-mo courses
Tuberculosis Research Center, Chennai (79)	South India	OFX vs EMB in daily intensive phase for 2 or 3 mo, followed by RIF-INH 2 times/wk for 0, 1, or 2 mo	3OHRZ, 3OHRZ/1HR 2 times/wk, 3OHRZ/2HR 2 times/wk, 2OHRZ/2HR 2 times/wk	3-mo intensive phase and at least 1-mo continuation are necessary to avoid >4% relapse
Burman et al. (12)	Africa, United States	MOX vs EMB 5 times/wk for first 2 wk and then 3 or 5 times/wk for a total of 8 wk	2EHRZ 5 times/wk/4HR, 2EHRZ 3 times/wk/4HR, 2MHRZ 5 times/wk/4HR, 2MHRZ 3 times/wk/4HR	**MOX improved sputum conversion at 4 and 6 wk;** no difference at 8 wk; 5 times/wk not better than 3 times/wk
Rustomjee (70), OFLOTUB, phase II	KwaZulu Natal, South Africa	EMB vs OFX, GAT, or MOX 6 times/wk	2EHRZ/4HR, 2OHRZ/4HR, 2GHRZ/4HR, 2MHRZ/4HR	**MOX accelerated early killing; MOX > GAT >OFX = EMB;** differences in sputum conversion not significant at 8 wk
Conde et al. (17)	Brazil	EMB vs MOX 5 times/wk for 2-mo intensive phase, 2 times/wk 4-mo continuation	2EHRZ/4HR, 2MHRZ/4HR	**MOX improved sputum conversion from 1 through 8 wk**
Dorman (22)	United States, Brazil, Spain, South Africa, Uganda	INH vs MOX 5 times/wk	2EHRZ/4HR, 2EMRZ/4HR	No differences in 8-wk conversions; logistical problems with multisite study
Wang (90)	Taiwan	Standard regimen vs standard regimen + MOX	2EHRZ/4HR, 2MEHRZ/4HR	**MOX showed shorter median time to sputum conversion and higher 6-wk conversion rate**
REMox, phase III	Asia, Africa, Mexico	MOX substituted for either EMB or INH and given for 4 mo of total therapy	2EHRZ/4HR,[c] 2MHRZ/2MHR, 2EMRZ/2MR	In progress
RIFAQUIN (8)	Southern Africa	MOX substituted for INH for 2 mo and then given with RFP[d] 2 times/wk for 2 mo or 1 time/wk for 4 mo high RFP	2EHRZ/4HR,[c] 2EMRZ/2M2P2, 2EMRZ/4M1P1	In progress
OFLOTUB, phase III	Africa	GAT substituted for EMB for 2 mo and then added to INH-RIF for 2 mo (for adults <65 yr old without history of diabetes or abnormal blood glucose)	2EHRZ/4HR,[c] 2GHRZ/2GHR	In progress

[a] In each regimen, the number represents the number of months of treatment: e.g., "3OHRZ/1HR" indicates 3 months of treatment with OHRZ followed by 1 month of treatment with HR. E, ethambutol (EMB); H, isoniazid (INH); R, rifampin (RIF); O, ofloxacin (OFX); Z, pyrazinamide; M, moxifloxacin (MOX); G, gatifloxacin (GAT); L, levofloxacin (LVX); P, rifapentine.
[b] Results in boldface indicate better outcomes with MOX.
[c] The standard control regimen is 2EHRZ/4HR.
[d] RFP, rifapentine.

bacteria, such as *S. aureus*, was marked by the rapid development of resistance (9). A high prevalence of FQ-resistant TB has been reported in populations such as Makati City, Philippines (34), and Mumbai, India (2), and the use of FQs as first-line therapy might mean that most MDR stains would show up as FQ resistant, thus eliminating the important contribution of the FQs to curing MDR TB and perhaps fostering the development of the fearsome extensively drug-resistant (XDR) TB (27, 28). XDR TB is MDR TB that is additionally resistant to any FQ as well as to any second-line injectable antibiotic—amikacin, kanamycin, or capreomycin.

While some FQ-resistant MDR TB probably results from the unfortunate practice of simply adding an FQ to a failing drug regimen (80) or giving an FQ with a regimen of weaker second-line drugs, there is also concern that they may fail as first-line TB drugs because of their success against other infections. In many countries, the FQs account for >10% of all antibiotics sold (50, 83) and are widely prescribed for common

infections at many sites: urinary and gastrointestinal tracts, paranasal sinuses, wounds, and sexually transmitted diseases (30). In addition, in many resource-poor countries, the FQs are not only frequently prescribed but also freely available without a prescription, as shown in a recent study from Tanzania (82). In a high-TB-burden country, a significant number of individuals with nascent or undiagnosed TB are likely to take an FQ, which could select for resistance in at least a fraction of the *M. tuberculosis* load they harbor (30).

RESISTANCE CAN DEVELOP AFTER SHORT COURSES OF FQs, BUT MAY BE LESS COMMON THAN FEARED

Unexpectedly, a very recent article (83) has shown that despite the wide availability and use of CIP in Tanzania, the prevalence of FQ-resistant *M. tuberculosis* was low and not related to a history of having recently taken a FQ. Only two (0.7%) of 291 isolates from newly diagnosed TB patients had FQ resistance, and these were not from the 22 (8%) patients who had taken an FQ within the previous 6 months (Table 2).

The lack of FQ resistance reported in this article seems like it must be an aberration, given the history of the rapid development of FQ resistance in other bacteria and reports such as those from Mumbai, India (2), where the prevalence of FQ-resistant TB increased from 3% in 1996 to 35% in 2004, paralleling the rise in general FQ use (Table 2). A report from Baltimore, MD, found FQ resistance in 2 of 19 (11%) patients exposed to FQs, although 1 had only borderline resistance (30). A study from Tennessee reported FQ resistance in an alarming 20.8% of patients exposed to FQs for >10 days, 60 days prior to a TB diagnosis, but in only 1.6% of those taking an FQ for <10 days (20). A report from Canada found FQ resistance in 3/20 patients exposed to FQs, but all 3 had received more than one course of an FQ (50).

However, several other studies looking for FQ resistance and its relation to previous FQ exposure found a low prevalence (Table 2). A report from Korea found 2.6% FQ resistance in patients exposed to FQs, but 3.4% resistance in those with no FQ exposure (60). A report from Taiwan found no correlation of FQ resistance with either FQ exposure or duration of FQ exposure, but saw a positive correlation with previous anti-TB treatment and resistance to any other drug (89). A survey from Tunisia found only 0.8% FQ resistance (73). A similar study in Rwanda found only one isolate with FQ resistance (0.2%) out of 616 new TB cases (81), but in the 8 cases of MDR TB previously treated with CIP, 3 were FQ resistant. A study from South Africa found gyrase mutations in only 1/201 patients exposed to FQ, but most had very short exposures—57% for only 1 day (42).

These reports of low numbers of FQ-resistant TB isolates in FQ-exposed patients are surprising, as resistance can clearly develop after routine courses of these antibiotics. The patient carrying the one non-MDR TB Rwandan strain with FQ resistance had received less than 14 days of therapy with OFX for respiratory symptoms, and other studies have described FQ resistance developing after taking an FQ for only 8 days (42) or 13 days (30, 32). When a patient presents with respiratory symptoms, it is common for the physician to prescribe 7 to 14 days of a broad-spectrum antibiotic, often an FQ, and only order a TB smear if the patient fails to improve. In fact, the Infectious Diseases Society of America (53) recommends using an FQ for community-acquired pneumonias in older patients or those with other complicating illnesses such as diabetes. If the patient actually has TB, they will effectively be receiving FQ monotherapy (31). A very recent investigation found that TB patients who also have chronic obstructive pulmonary disease (COPD) have an increased risk of having FQ-resistant TB, presumably because they were treated with FQs for symptoms thought to be related to their COPD (48). A study that looked at isolates from sputa taken both before and after a course of FQs given for nonspecific respiratory symptoms found that 1 of 18 patients (5.5%), developed FQ resistance after taking an FQ for only 7 days (88).

GYRASE MUTATIONS CONFER FQ RESISTANCE, BUT SOME MAY BE TREATABLE WITH MOX OR NEWER QUINOLONES

Curiously, the two FQ-resistant strains described in the study from Tanzania (83) were found in patients with no history of recent FQ exposure. One of the two strains was resistant to CIP but only intermediately resistant to MOX and had a valine substitution for the alanine at GyrA amino acid 90. This substitution was also reported in two other studies that each found a single strain with a gyrase mutation (43, 50). The fluoroquinolones inhibit the DNA gyrase (54), and ~50 to 90% (40, 89, 92) of FQ-resistant strains have mutations in the *gyrA* gene that result in substitutions in amino acids 89, 90, 91 or 94 (95) of the GyrA subunit. Less common substitutions have been reported in amino acids 88 (32), 74 (46), and 80, but the association of substitutions in amino acid 80 with FQ resistance has been questioned (7, 87). Substitutions in the other gyrase subunit, GyrB, have been found in up to 10% of FQ-resistant isolates of *M. tuberculosis* (18) but generally confer low-level resistance that may be susceptible to treatment with high-dose MOX (64).

It was previously observed that strains with the GyrA Ala90Val substitution, such as the Tanzanian strain (83), are sometimes only intermediately resistant to MOX (87), and studies with mice suggest that MOX might even contribute to the cure of XDR-TB strains with this mutation (64). A recent study found that the novel isothiazoloquinolone ACH-702 had even better activity than MOX against strains with this substitution and also inhibited a strain with a substitution at amino acid 94 (65), the most commonly mutated site. Unfortunately, there is no isothiazoloquinolone currently suitable for clinical use, but other new quinolones have been described that may be more active against TB than MOX (3). While it was thought that once a strain has a GyrA mutation it is resistant to all FQs, this may not be true for all GyrA mutations nor for all quinolones (52).

FQ RESISTANCE WITHOUT GYRASE MUTATIONS

The other FQ-resistant strain in the Tanzanian study (83) was isolated from an HIV-positive patient with a very low CD4 cell count. It had no gyrase mutation, was only intermediately resistant to CIP (MIC, 1 μg/ml) and was sensitive to MOX. Studies screening for FQ resistance have found that up to 50% or more of FQ-resistant strains don't have gyrase mutations

TABLE 2. Studies reporting prevalence of FQ resistance in non-MDR TB[a]

Study (reference)	Site	Population	Finding(s)	Mutations
Riantawan et al. (67)	Thailand	Cardiothoracic center	Initial resistance to OFX in 1.1% of 1,738 new cases of pulmonary TB; acquired resistance to OFX in 8.1% of 123 previously treated patients	Not studied
Casal et al. (13)	Spain	Hospital strains	213 strains susceptible and resistant to other drugs; OFX MIC, 1 μg/ml in 22% and 2 μg/ml in 6.1%	Not studied
Hemvani et al. (37)	Central India	Hospital lab isolates	1,426 strains; Cip^r, 3.6%	Not studied
Grimaldo et al. (34)	Makati City, Philippines	Hospital isolates	FQR with no other resistance, 1989–1994, Cip^r/Ofx^r, 1%/0%; 1995–2000, Cip^r/Ofx^r, 17.4%/24.4%; FQR and MDR, 1989–1994, Cip^r/Ofx^r, 10.3%/24%; 1995–2000, 51.4% both	Not studied
Ginsburg et al. (30)	Baltimore, MD	Newly diagnosed TB patients	FQR without FQ in previous 6 mo, 0/36; FQR with FQ, 2/19 (both AIDS patients with CD4 count <50; (i) patient 1, 6 days LVX + 7 days CIP; (ii) patient 2, 3 courses of GAT)	(i) Patient 1, resistant to all FQs, GyrA G88C; (ii) patient 2, intermediate resistance (not studied)
Bozeman et al. (11)	United States	Trial strains (Rif^s); strains referred to CDC	From TB trials, 2/1,373 Cip^r; CDC: 1996–2000, 33/1,852 (1.8%) Cip^r, 25/33 (75.8%) in MDR	26/30 had GyrA substitutions and 4/30 had no GyrA substitutions
Huang et al. (40)	Taiwan	Tertiary hospital, 1995–2003	FQR in pan-sensitive strains, 1995–2003, <2%; in MDR 1995–1997, 8%; in MDR 1998–2003, 20%	Of 10 FQR, 1 A90V, 3 D94G, 1 G88A D94Y, 5 GyrA WT, all GyrB WT
Wang et al. (88)	Taiwan	Newly diagnosed TB patients	9 patients with isolates before and after FQ; 1 developed resistance to OFX	Not studied
Park et al. (60)	Seoul, South Korea	From records of hospital microbiology	FQ exposed: Ofx^r in 1/39, but primary MDR TB; Ofx^r in 1.1% of newly diagnosed patients and 8.5% in patients retreated	Not studied
Umubyeyi et al. (81)	Rwanda	Resistance survey	In 616 new cases, 1 Ofx^r and received <14 days FQ for respiratory symptoms; in 32 MDR, 3 Ofx^r and all received CIP as prior TB treatment	1 GyrA D94A, 3 GyrA T80A
Wang et al. (89)	Taiwan	Randomly selected isolates from tertiary facility	420 isolates, 14 FQR (3.3%), no statistical association with previous FQ; statistical association with previous TB treatment and any other drug resistance; 28 FQS strains, no mutations	14 FQR: GyrA, 4 D94G, 1 A90V; GyrB, 1 N538D; 8 WT GyrAB (lower avg. MICs)
Agrawal et al. (2)	Mumbai, India	Tertiary facility strains with DST requested	1995–2004, MDR increased from 32% to 56%; Cip^r (8 μg/ml) increased from 0% to 35%	Not studied
Devasia et al. (20)	Tennessee	TB patients covered by drug benefit plan	37% had FQ: <10 days, FQR in 1/62; with FQ >10 days, FQR in 7/54 (13%); most had FQR when FQ given >60 days before TB diagnosis	Not studied
Long et al. (50)	Canada	TB patients covered by drug benefit plan	428 patients, 54 with single FQ prescription, no FQR; 20 patients with multiple FQ prescriptions, 3 FQR	1 GyrA A90V, 2 WT GyrA; CIP MIC, ≥4; all GyrB WT
Xu et al. (92)	Shanghai, China	TB reference lab	FQR in 1.9% in pan-sensitive, statistical association with FQR with resistance to 1st-line drugs and prior TB treatment	*gyrA* mutations in 81.5% of Ofx^r strains; mutations not specified
Soudani et al. (73)	Tunisia	University hospital, all isolates 2005–2008	Cip^r (MIC, 2 or 4 μg/ml) in 4/495 isolates (0.8%); 3 new cases, 1 previously treated MDR	1 GyrA I92M, 1 A90L; 2 WT GyrA; all GyrB WT
Jeon et al. (42)	South Africa	Gold miners	440 TB patients with FQ <1 yr prior to TB diagnosis, most 1 day of FQ; only looked for *gyrA* mutations; 1 with GyrA change	1 GyrA A90V in patient with multiple FQ use for a total of 8 days
Hu et al. (39)	Rural east China	Pulmonary TB registered patients	FQR in 31/351 strains, statistical association of FQR with treatment of respiratory illness, borderline with Beijing genotype; no statistical association with other drug resistance	17/31 with GyrA substitutions, 3 with 2; 1 in GyrB, WT GyrA = lower FQ MICs
van den Boogaard et al. (83)	Tanzania	Culture-positive TB patients	291 cultures; no resistance in 22 with FQ in previous 6 mo; 2 FQR isolates in non-FQ-exposed patients	1 Cip^r, MOX intermediate, GyrA A90V; 1 CIP intermediate, Mox^s, GyrA WT

[a] WT, wild type (no mutations); FQS, FQ sensitive; FQR, FQ resistant; DST, drug sensitivity testing.

(40, 50, 89). Work *in vitro* has shown that low-level FQ resistance in mycobacteria can be caused by efflux pumps such as antiporters LfrA (77) and Tap (1, 4), as well as the ATPase complex Rv2686c-Rv2687c-Rv2688c (62). It was also recently reported that the MICs for OFX rise due to the induced expression of efflux pumps when *M. tuberculosis* is exposed to rifampin (51) and also when *Mycobacterium marinum* enters macrophages (1). Perhaps the role of efflux pumps in the development of both tolerance and resistance to the FQ may be more important than has been appreciated.

Increased expression of the conserved mycobacterial pentapeptide MfpA also causes FQ resistance *in vitro* (85), similar to the resistance conferred by the plasmid-borne Qnr pentapeptide proteins in Gram-negative bacteria (74). However, no non-gyrase mutation has yet been documented to be responsible for FQ resistance in clinical isolates of *M. tuberculosis*, so the mechanisms involved in "resistant" isolates with unmutated gyrases and their clinical importance are unclear. However, as FQ resistance develops in a stepwise fashion, low-level resistance may allow the strains to grow near the end of the dosing interval or with poor compliance and accumulate additional mutations, such as a first or a second mutation in *gyrA* (87) that results in high-level resistance (23) not susceptible to even the most active quinolones.

In terms of the MPC paradigm (23), the presence of even a low-level first mutation could raise the MPC above the obtainable or toxic tissue drug concentration for MOX, making additional mutations likely. The MPC concept is based on mutation frequencies derived from *in vitro* bacteria exposed only to an FQ, and the frequencies would presumably be lower when the FQs are given together with other effective drugs, such as rifampin and pyrazinamide. However, it seems that FQ resistance can develop in the context of multidrug therapy, as shown by several studies that found an association between resistance to FQs and resistance to any drug, especially multidrug resistance (Table 2). It is possible that the frequent development of FQ resistance during the treatment of MDR TB could be a result of the other second-line drugs used being less effective than rifampin and pyrazinamide, and in addition, some strains develop resistance to them.

Studies looking at the FQ MICs of many pan-susceptible clinical isolates have found something approximating a bell-shaped distribution, with 8-fold differences in the MICs of "sensitive" strains (6). Perhaps some strains with low-level resistance, which is often just above the resistance-defining cutoff, in patients without previous FQ exposure simply represent the high MIC tail of this distribution. The reasons for these MIC differences, their clinical significance, and their relationship to the development of higher-level FQ resistance are all unknown. Alternatively, it is possible that reporting or memory error was a factor in some of the surveys of FQ resistance and that the patients or the people from whom they contracted the disease had actually taken an FQ. It is also conceivable that the low-level, non-gyrase resistance found in some strains was not present in the original isolates, but rather was the result of spontaneous mutations selected when the strains were plated on FQ-containing medium as part of the resistance testing. It is therefore important to use a quantitative assay such as the proportion method, but the interpretation can be complicated by the phenomenon of heteroresistance, where resistance is present in a minority of greater than 1% of colonies, or PCR of the *gyrA* gene amplifies both mutated and unmutated sequences. This is presumed to be due to emerging resistance or infection with multiple strains (84).

GIVING AN FQ FOR NONSPECIFIC RESPIRATORY SYMPTOMS DELAYS TB DIAGNOSIS AND THERAPY

If the use of FQs for nonspecific respiratory symptoms or presumptive community-acquired pneumonia could be curtailed, it would reduce concerns about the development of FQ-resistant TB, but would also have additional benefits. Several studies have shown that taking >5 days of an FQ in the previous months results in delays of 2 to 5 weeks in initiating anti-TB therapy (15, 21, 33, 96). OFX, LVX, or MOX taken for respiratory symptoms that are actually TB will kill off some of the bacilli and may result in a transient improvement, but when the patient returns with a recrudescence of the symptoms, there will be fewer bacilli, which means that sputum smears are more likely to be negative (42) and the sputum cultures will take longer to turn positive. Consequently, in the elderly or patients with complicating illnesses such as diabetes, taking an FQ in the months prior to TB diagnosis has been associated with increased mortality (88).

SUMMARY: CAUTIOUS OPTIMISM ON THE FUTURE OF QUINOLONES AS FIRST-LINE ANTI-TB THERAPY

What then is the future for the FQs in the treatment of TB, beyond their current importance in the treatment of MDR TB? While four studies showed that MOX improved early bacterial killing, only one (17) showed a statistically significant improvement in the percentage of sputa that had converted to negative at 8 weeks (Table 1). If early sputum conversion, particularly at 8 weeks, is a reliable indicator of cure, there is some enthusiasm that first-line treatment containing MOX may be able to cure pan-sensitive TB in less than 6 months, perhaps with ethambutol reserved for treatment of MDR strains. As the FQs are bactericidal, while ethambutol is only bacteriostatic, they may be more effective at preventing the spontaneous emergence of MDR TB, especially in isoniazid-monoresistant strains (16). However, without proven biomarkers, the true effectiveness of a MOX-containing shorter treatment regimen cannot be evaluated until at least 6 to 12 months after patients in phase III trials complete therapy. The lack of a significant improvement when MOX was substituted for isoniazid was a disappointment, but another evaluation is currently in progress (Table 2). There are also other new anti-TB drugs in clinical trials, and preliminary studies have suggested that if these were combined with MOX, it might be possible to further shorten first-line therapy or perhaps reduce the duration of treatment required to cure multiresistant strains (56, 86, 91).

A high prevalence of FQ-resistant TB has likely voided the possibility of first-line FQ treatment in some communities (2), but it might still be viable in areas with a low prevalence of FQ-resistant TB, such as Tanzania, where the widespread availability and use of FQs for other infections have not led to a high prevalence of FQ-resistant TB (83). While such reports are encouraging, caution still seems warranted in light of doc-

umented cases of FQ resistance developing after taking an FQ for as few as 7 (88) to 8 (42) days.

It appears that limited FQ exposures may select predominantly for low-level resistance that may be treatable with high-dose MOX (64) or a future, highly effective quinolone (65): the strains either lack *gyrA* mutations (50, 89); have the Ala90Val substitution (42), the mutation yielding the lowest resistance of all common GyrA mutations (87); have the Thr80Ala GyrA substitution, which is not clearly related to FQ resistance (7, 81); or have a mutation in *gyrB* (89). It is worrisome though that some of these low-level-resistant strains were unexplainably found in patients with no history of FQ exposure (60, 83). If susceptibility tests use CIP or OFX, the strains judged to be resistant to these drugs may still be sensitive to MOX, and clinical outcomes, even with XDR-TB, may improve if MOX is included in the drug regimen (41).

If a MOX-containing shorter course is proven effective, its implementation might be recommended only where the prevalence of FQ-resistant TB is low and FQs are not routinely used for nonspecific respiratory symptoms. Curtailing the use of FQs to treat respiratory symptoms when TB cannot be effectively excluded by keen clinical judgment or a highly sensitive diagnostic test (36) would reduce concerns about the development of resistance and also eliminate the delays in initiating TB therapy that occur when FQs are inadvertently administered as TB monotherapy (15).

THE DOWNSIDE: SOME REASONS FOR NOT USING FQs AS FIRST-LINE AGENTS

There are a few negative aspects that need to be considered before an FQ-containing first-line regimen could be broadly recommended. The FQs are fairly good drugs for common nonspecific respiratory syndromes and community-acquired pneumonia, and eliminating this usage to ensure they remain effective as first-line TB therapy may not prove beneficial to all-cause morbidity and mortality at the community level. Also, using FQs as standard first-line therapy would reduce their effectiveness against MDR TB, and could perhaps result in the appearance of more XDR TB. Finally, the cost of the FQs must be considered. In developing countries, the standard drug regimen of rifampin, isoniazid, ethambutol, and pyrazinamide can cost less than $20 for the entire 6-month treatment, which is about the current cost of a 5-day course of MOX. Even though an effective shorter course of TB therapy would reduce the burden on health care infrastructure, unless the price of a MOX-containing regimen is relatively comparable to that of the standard drug regimen, a cost-benefit analysis is not likely to justify its implementation in the resource-poor countries where most of the world's TB occurs.

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