Newer Fluoroquinolones for the Treatment of Tuberculosis

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The newer fluoroquinolones—levofloxacin, moxifloxacin and gatifloxacin—have potent bactericidal and sterilizing activities against *Mycobacterium tuberculosis*. Thus, they have the potential value in managing both drug-susceptible tuberculosis and drug-resistant tuberculosis, including the possibility of shortening the duration of treatment. The emergence of more “difficult” drug-resistance scenarios—fluoroquinolone-resistant multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis, pose a challenge to the global control of tuberculosis. The newer fluoroquinolones might also have clinical efficacy in some of the patients with such forms of the disease, perhaps reflecting partial bacillary cross-resistance only among the fluoroquinolones, and/or different optimal critical concentration cut-offs to define bacillary resistance to different fluoroquinolones. In summary, more experience is needed regarding the utility of newer fluoroquinolones for the treatment of tuberculosis.

Introduction
Quinolones are synthetic drugs developed by structural modification of the 4-oxo-1,4 dihydroquinolone nucleus or the 1,8 naphthyridine nucleus. Fluorination of these basic molecules, usually at position 6, resulted in the fluoroquinolones. The term “newer fluoroquinolones” generally refers to three drugs—levofloxacin, moxifloxacin and gatifloxacin. Levofloxacin is the S(-) enantiomer of the parent racemic compound ofloxacin, whereas moxifloxacin and gatifloxacin are generally regarded as later-generation C-8-methoxy fluoroquinolones. These three newer fluoroquinolones have potent antituberculosis activity, much of which is due to the C-8-methoxy moiety (1–3).

An early, comprehensive review (on clinical trials, cohort studies and case reports) addressed the efficacy of fluoroquinolones in tuberculosis, together with patient tolerability/safety, for the following indications—(i) first-line treatment of drug-susceptible pulmonary tuberculosis, (ii) first-line treatment of multidrug-resistant (MDR) tuberculosis and (iii) treatment of patients with intolerance to standard first-line antituberculosis drugs (4). The data were insufficient to support the use of older fluoroquinolones, especially ciprofloxacin, as substitute agents for drug-susceptible or drug-resistant tuberculosis. This view was also shared by a systematic review of fluoroquinolones used for treating tuberculosis (5).

In this present short article, the possible role of fluoroquinolones in treating tuberculosis discussed is largely restricted to levofloxacin, moxifloxacin and gatifloxacin.

Newer fluoroquinolones for the treatment of MDR tuberculosis
An early prospective study of MDR tuberculosis has demonstrated the dose-dependent efficacy of ofloxacin in the treatment of this disease and the 800 mg once-daily dose was found to be superior to the 300 mg once-daily dose, achieving a more rapid and higher proportion of culture negativity (6). Over the last decade, other reports on the use of fluoroquinolones (largely ofloxacin and ciprofloxacin) for the treatment of MDR tuberculosis have emerged (7–12), with success (cure + treatment completion) rates generally around 70%.

The great variation in treatment outcomes could well be due to the analytical methodology, the definition of success and failure, the drug susceptibility testing methodology, the thoroughness of clinical follow-up and the availability of data. In a retrospective study from Hong Kong, radiographic cavitation, bacillary resistance to ofloxacin and
poor patient adherence were found to be independently associated with adverse treatment outcomes (8). In the USA, a large study on 205 patients with MDR tuberculosis has shown that the use of fluoroquinolones was independently associated with improved initial microbiological outcome, as well as survival from all causes of death (13). These findings suggest the likely pivotal role of the fluoroquinolones in the chemotherapy of MDR tuberculosis.

In a study in Bangladesh that evaluated six standardized treatment regimens for MDR tuberculosis, among consecutive cohorts of patients (14), the final most effective treatment regimen required a minimum duration of nine months with gatifloxacin, clofazimine, ethambutol, and pyrazinamide throughout, supplemented by prothionamide, kanamycin and high-dose isoniazid during an intensive phase of a minimum of four months, giving a relapse-free success rate of 87.9% in 206 patients. The treatment success rate for the earlier ofloxacin-containing regimen was only 69.0% (15).

In the mouse model of tuberculosis, the combination of amikacin, ethionamide, moxifloxacin and pyrazinamide has shown good efficacy (2, 16). In one observational study, regarding the use of moxifloxacin for MDR tuberculosis, the treatment success rate was only 51.7% (17). In another similar anecdotal report, there was no clear documentation of the chemotherapy response rate for several patients with MDR tuberculosis (18).

The optimal duration of treatment for MDR tuberculosis using a fluoroquinolone-containing regimen is currently unknown. A systematic review and meta-analysis has shown that the proportion of patients treated successfully improved when the length of treatment was at least 18 months, and if patients received directly observed therapy throughout (19). There is, however, a suggestion that some patients could be adequately treated with newer fluoroquinolones for shorter periods to achieve a relapse-free cure (8, 14). More detailed evaluation is required using randomized controlled trials (20).

Fluoroquinolone resistance in Mycobacterium tuberculosis can emerge following the injudicious use of this class of drugs, especially in the setting of MDR tuberculosis, alongside the suboptimal use of accompanying drugs too few in number and/or too low a dosage (21-23). Poor drug quality can also be an issue. Overzealous use of fluoroquinolones in the treatment of infections of the lower respiratory tract and other origins, particularly in the community, might also contribute to the development of fluoroquinolone-resistant tuberculosis (24). As aminoglycosides/capreomycin also have potent antituberculosis activity, the “loss” of these second-line injectable preparations together with fluoroquinolones, through their suboptimal use in the management of MDR tuberculosis, would result in the development of extensively drug-resistant (XDR) tuberculosis (25, 26). This latter disease poses an even more “complicated” scenario of drug resistance than fluoroquinolone-resistant MDR tuberculosis, and is generally associated with a treatment success rate of 50% or less (26, 27). A recent analysis of the treatment outcomes and survival based on drug resistance patterns in MDR tuberculosis strongly underscores the appropriateness of the definition XDR tuberculosis and its association with a dismal prognosis (28).

An observational study has shown the potential usefulness of levofloxacin in treating drug-resistant tuberculosis (29). In a cohort study, a comparison between ofloxacin and levofloxacin (30) has also revealed that the latter fluoroquinolone, when substituting for the former, in regimens with similar accompanying drugs, resulted in higher success rates for both ofloxacin-susceptible (96.2% vs. 87.5%) and ofloxacin-resistant (78.6% vs. 45.5%) MDR tuberculosis in the treatment of adherent patients. Thus, levofloxacin is quite likely to be more efficacious than ofloxacin when included in multidrug regimens for treating MDR tuberculosis, including the “difficult” forms.

The C-8-methoxy fluoroquinolones—moxifloxacin and gatifloxacin—might also have activity against ofloxacin-resistant M. tuberculosis isolates, including those that are MDR, notwithstanding the phenomenon of partial cross-resistance among members of the fluoroquinolone class (31-34). Standardization of the methodology of drug susceptibility testing for second-line antituberculosis drugs might be of greater clinical and microbiological relevance (35). Indeed, these two newer fluoroquinolones have lower mutant prevention concentrations for M. tuberculosis and thus, theoretically, should have a greater potential to restrict the development of bacillary resistance (36). However, it appears that for efficient suppression of development of drug resistance in M. tuberculosis, high-dose moxifloxacin is preferable, but this approach could well be limited by intolerability (37). Treatment with moxifloxacin in patients with XDR tuberculosis in South Africa has been found to have a favourable impact on the survival—hazard ratio: 0.11 (95% confidence interval [CI]: 0.01–0.82) (38). In a recent systematic review and meta-analysis on the treatment outcomes of patients with XDR tuberculosis (39), among 560 patients, 43.7% exhibited a cure or treatment completion. Random
Newer fluoroquinolones for the treatment of drug-susceptible tuberculosis

The most commonly encountered indication for the use of fluoroquinolones in current practice is intolerance to standard first-line antituberculosis drugs, especially due to hepatic dysfunction (4). Although some patients can be satisfactorily returned to the originally scheduled first-line drug regimen, most affected patients require the use of a relatively non-hepatotoxic regimen, on an interim or definitive basis (40, 41). Earlier reports on this subject largely involved ofloxacin, used in conjunction with streptomycin, and ethambutol (42, 43). In case of definitive treatment of tuberculosis, ofloxacin/levofloxacin can be used together with isoniazid/rifampicin, plus perhaps even low-dose pyrazinamide, depending on the liver reserve (40, 43). In a retrospective study of a cohort of tuberculosis patients with liver injury, prescribed an alternative therapeutic regimen consisting of three months of streptomycin, ethambutol and ofloxacin, followed by nine months of ethambutol and ofloxacin, this alternative regimen proved well tolerated by the patients, and was effective in 85% (44). In another study (45) involving patients who developed hepatotoxicity to first-line antituberculosis drugs, the use of levofloxacin and moxifloxacin caused no additional hepatic insult, and allowed smooth normalization of liver transaminases similar to the control patients.

Hepatotoxicity due to first-line antituberculosis drugs has been found to be particularly frequent among patients with solid-organ transplants (46–48), perhaps largely due to immunocompro-mization and the toxicity of anti-rejection drugs. The use of regimens containing ofloxacin/levofloxacin was especially beneficial. Aside from good tolerance, the lack of drug interactions proved to be advantageous. There is a recent report on the beneficial use of moxifloxacin in treating tuberculosis in human immunodeficiency virus (HIV)-infected patients when conventional regimens could not be used (49).

Other serious intolerance to standard first-line antituberculosis drugs is rare. Important examples include agranulocytosis (50), thrombocytopenia (51) and renal failure (52). Levofloxacin use in these patients has produced a good outcome.

Aside from intolerance to conventional antituberculosis drugs, the newer fluoroquinolones may find a place in increasing the efficacy of antituberculosis drug regimens due to their potent activity. An early study has not shown that adding levofloxacin to a standard four-drug regimen improved the eight-week culture response (53). However, an interesting case report demonstrated the rapid improvement of intracranial tuberculomas after addition of ofloxacin to the first-line antituberculosis drug regimen (54). In theory, ofloxacin/levofloxacin penetrates the pleural cavity better than rifampicin (by more than 10-fold) and, thus, helps to strengthen the first-line chemotherapy for tuberculous empyema (55–57), although concrete clinical data to support such efficacy following the addition of a fluoroquinolone to the treatment is lacking.

In the murine model of tuberculosis, moxifloxacin-containing regimens demonstrated a greatly reduced time to culture conversion (58), and a short treatment with such a regimen produced a stable cure (59). Based on these findings, the significant sterilizing activity of moxifloxacin might enable a shortening of the length of therapy for drug-susceptible tuberculosis. In early 2000s, a report from India suggested the potential usefulness of ofloxacin for shortening the length of treatment of drug-susceptible tuberculosis (60). In a study initiated by the Centers for Disease Control and Prevention, Tuberculosis Trials Consortium (CDC TBTC) the addition of moxifloxacin to isoniazid, rifampicin and pyrazinamide did not affect the two-month sputum culture status, but there was increased activity at earlier time points (61). In a similarly designed study (62), using serial sputum colony counting by non-linear mixed effects modeling, moxifloxacin substitution for ethambutol appeared superior during the early phase of a bi-exponential fall in colony counts, but a significant and similar acceleration of bacillary elimination during the late phase occurred with both moxifloxacin and gatifloxacin. In another study undertaken in Brazil, at eight weeks, culture conversion to negative occurred in 80% patients in the moxifloxacin group, compared with 63% patients in the ethambutol group (difference 17.2%, 95% CI: 2.8–31.7) (63). A follow-up study of the CDC TBTC substituting moxifloxacin for isoniazid only showed a non-significant
increase in sputum culture conversion at week 8 (64).

A smaller study has also shown that adding moxifloxacin to the four standard first-line antituberculosis drugs shortened the time to culture conversion, and the culture conversion rate after six weeks of treatment rose from 61% to 82% (65).

A randomized controlled trial, called REmoXB, is now underway to see whether substitution of moxifloxacin for isoniazid can reduce the current length of chemotherapy of drug-susceptible tuberculosis to four months (http://clinicaltrials.gov/ct2/show/NCT00864383). The OFLOTUB consortium is also investigating a four-month regimen based on gatifloxacin.

Although an early bactericidal activity (EBA) study has shown significant results with moxifloxacin in patients with pulmonary tuberculosis (66), another such study addressing the early and extended EBA of levofloxacin, alongside that of moxifloxacin and gatifloxacin, has shown that levofloxacin 1,000 mg daily produced potent EBA comparable with that of isoniazid, and better than that of moxifloxacin and gatifloxacin (67). Weekly moxifloxacin and rifapentine has been shown to be more active than twice-weekly rifampicin and isoniazid in a mouse tuberculosis model (68). In another murine model of tuberculosis, daily dosing of rifapentine cured the disease in three months or less (69). A randomized controlled clinical trial using high-dose rifapentine and moxifloxacin (RIFAQUIN) is now in progress (http://www.ipc.rxgenomics.org/inter.tb/intertb_trials.htm).

Safety/tolerance of newer fluoroquinolones
In a case-control study, the rate of any major adverse events in those who used levofloxacin (because of drug-resistant tuberculosis or intolerance to first-line antituberculosis drugs) was almost half that in those who received standard chemotherapy (rate ratio: 0.60, 95% CI: 0.44–0.82) (70). Furthermore, there was no difference between the levofloxacin and control arms with respect to central nervous system, gastrointestinal (GI) tract, skin or musculoskeletal related events when adjusted for the concomitant drugs. These findings strongly corroborate those from observational and other studies of the levofloxacin treatment of tuberculosis (29, 30). However, it might be useful to remember some rare side effects related to ofloxaclin/levofloxacin use including arthropathy (71), fungal superinfection (72) and antibiotic-related colitis (73). In retrospective cohort and nested case-control analyses involving hospitalized patients with tuberculosis treated with fluoroquinolones, the risk of Clostridium difficile-associated di-

arrhoea was found to be modest after controlling for sex, age, other antibiotic use, serum albumin, duration of hospital stay and nasogastric feeding (74).

The commonest side effects of moxifloxacin use are GI disturbance and neurological dysfunction (17, 18, 61, 64). Although the risk for potential cardiotoxicity is perhaps higher for moxifloxacin, compared with levofloxacin (75, 76), a randomized trial involving the cardiac rhythm safety of moxifloxacin versus levofloxacin in elderly patients with community-acquired pneumonia has shown them to have a comparable risk and safety (77). However, it is important to remember that this may not be the case when considering long-term use of these fluoroquinolones in the treatment of tuberculosis. Extreme caution must be exercised in patients with underlying cardiac diseases or QTc prolongation, especially for those with risk factors for torsades de pointes (78).

Gatifloxacin use is associated with GI and neurological adverse reactions like moxifloxacin. It also has potential cardiotoxicity (75, 76, 78). However, most importantly, it is associated with dysglycaemia (79), especially in older patients. As the result of a warning from the Food and Drug Administration in the USA, manufacture of this fluoroquinolone has in fact ceased in that country since 2006.

Other issues regarding the use of newer fluoroquinolones in tuberculosis
Despite the promise of the newer fluoroquinolones in the future treatment of tuberculosis, such optimism is somewhat tempered by the escalating rates of fluoroquinolone resistance in M. tuberculosis in many parts of the world, especially in countries with a high incidence of tuberculosis (80, 81). Empirical use of the newer fluoroquinolones may also mask the diagnosis of tuberculosis, with a resultant delay in the start of treatment and a poor outcome (82, 83). One study from the USA has, however, shown no impact regarding the appearance of culture-negative tuberculosis (84).

Another concern is the interaction of moxifloxacin and gatifloxacin with rifampicin, resulting in potential attenuation of the efficacy of the former fluoroquinolone (85), and a potentially increased risk of toxicity for the latter fluoroquinolone (86). More detailed evaluation is needed in this area.

On the bright side, there are, however, newer delivery vehicles, such as hyaluronic microspheres as carriers of the newer fluoroquinolones to enable better targeting and effectiveness in pulmonary tuberculosis (87). In addition, there is pre-
liminary evidence that levofloxacin might have immunomodulating potential in addition to antimycobacterial activity and, if properly harnessed, this could have therapeutic implications (88).

Conclusions
The newer fluoroquinolones have good bactericidal and sterilizing activities against *M. tuberculosis*. They could support the existing antibiotic armamentarium for the therapeutic control of drug-resistant and drug-susceptible tuberculosis. The potential adverse aspects associated with their use in the disease merit further exploration and evaluation in order to develop optimum regimens.

References


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