The Safety of Levofloxacin in Tuberculosis Treatment Including Drug-induced Hepatotoxicity

Introduction
The fluoroquinolone class of antibacterial agents is one of most prescribed in the world (1). Some quinolones, such as ciprofloxacin, levofloxacin, moxifloxacin and gemifloxacin, are relatively safe and well tolerated, but a number of fluoroquinolones have been withdrawn from the market due to poor tolerability or severe adverse events (2). Levofloxacin, a third generation fluoroquinolone, is the active enantiomer of ofloxacin and exhibits very similar pharmacokinetic behavior to ofloxacin (3). Most common adverse events involving levofloxacin are gastrointestinal (GI)-related or central nervous system (CNS) events and rarely result in treatment discontinuation (4). Levofloxacin can induce a mild, usually transient, elevation of hepatic enzymes like other fluoroquinolones (5), but the incidence of acute liver failure is relatively low compared with moxifloxacin and gatifloxacin (6).

Tuberculosis continues to be a significant health problem throughout the world. Combination therapy is necessary for short-course antituberculosis treatment, but this increases the risk of adverse drug events significantly including hepatotoxicity. Fluoroquinolones are frequently used to replace first-line antituberculosis agents in multidrug-resistant tuberculosis patients or as a substitute drug for those patients who are unable to tolerate first-line drugs. Levofloxacin as, like other new fluoroquinolones, exhibits high bactericidal activity against Mycobacterium tuberculosis. Although the safety profile of levofloxacin when used in short-course treatment for bacterial infections has been well-established, its safety in tuberculosis treatment, especially after first-line antituberculosis drug-induced hepatotoxicity, is unclear. A comprehensive review of the medical literature has identified six publications including three small randomized controlled trials and two written in Chinese evaluating the use of levofloxacin in tuberculosis treatment and the reported adverse events. The findings of these studies showed non-inferiority and the adverse events did not increase even after adding levofloxacin to other antituberculosis drugs. The use of levofloxacin after hepatitis induced by antituberculosis drugs produced no additional hepatotoxicity. The published data support the safety of levofloxacin use in tuberculosis treatment and even after first-line antituberculosis drug-induced hepatitis. Further trials with large patient numbers are necessary to evaluate the efficacy and safety of levofloxacin in the management of tuberculosis.
Materials and methods

The PubMed search engine was used to query the National Library of Medicine database using the following search terms “levofloxacin” and “tuberculosis,” combined with “adverse event,” “complication” or “hepatotoxicity.” This query was limited to English-language publications and clinical studies. The contents of this review include studies available until July 2010. The same search criteria were used to query the Cochrane Database of Clinical Trials. All publications of either randomized controlled trials or retrospective studies of levofloxacin in treating tuberculosis were included. The citations of all included publications were also considered for inclusion in this review.

Results

The PubMed query identified five publications that met the inclusion criteria (11, 18, 20, 21). However, one of these publications reported the finding of a subset of patients (small number) and all the data were also subsequently published with the results of a later report (11, 19). Only the latter publication was included in this review. Review of the cited publications yielded four additional, previously unidentified publications written in Chinese, but only two met the inclusion criteria (22, 23). There were other two small randomized controlled trials evaluating the clinical efficacy of combined levofloxacin plus capreomycin and levofloxacin, pasiniazide plus Mycobacterium vaccae in multidrug-resistant (MDR) tuberculosis patients (24, 25).

Table 1 summarizes the design of the trials reported in these publications (11, 19–21) while Table 2 summarizes the results of the trials published in Chinese (22, 23). Three publications reported the findings of randomized controlled trials (18, 22, 23). One was a retrospective study (11), one was a case-control study (20) and the other was prospective observational study (21). All the studies focused on the levofloxacin use in tuberculosis patients and recorded the details of all adverse events except one study (Table 2) (23).

Overview of the study design

Two studies were conducted in the USA (18, 20), one trial in Hong Kong (11), one trial in Taiwan (21) and two trials in China (22, 23). Only one trial was a multi-center study (18) and the rest of the trials were all single-center studies (11, 20–23). In the three randomized controlled trials (18, 22, 23), no targeted sample size was reported.

Levofloxacin added to a regimen

Four of the six trials compared levofloxacin plus antituberculosis medication and antituberculosis medication alone (18, 20, 21, 23). These four studies included two randomized controlled trial (18, 23), one case-control trial (20) and one prospective observational trial (21).

Comparison of levofloxacin versus ofloxacin added to a regimen

Lu Y et al. conducted a randomized controlled trial which compared levofloxacin with ofloxacin in anti-tuberculosis first- and second-line regimens (22). Yew et al. compared levofloxacin with ofloxacin added to antituberculosis drugs for MDR tuberculosis in a retrospective trial (11).

Four of the six trials included HIV patients (18, 20–22) and only the trial by Yew et al. involved MDR tuberculosis patients who were se-
Safety of Levofloxacin in Tuberculosis Treatment

Levofloxacin added to a regimen

El-Sadr et al. examined levofloxacin added to a standard four-drug regimen and observed sputum culture conversion at eight weeks with treatment effectiveness. The results showed no benefit when levofloxacin was added to the existing therapy (18). Zhao et al. conducted a small randomized controlled trial examining the efficacy and safety of levofloxacin-containing regimens for patients undergoing retreatment of pulmonary tuberculosis. The negative sputum culture rates after two months with and without levofloxacin were 92.8% and 42.8%, respectively ($p < 0.05$), although there was no difference after four, six and nine months (23). Marra et al. focused on adverse events associated with adding levofloxacin and the treatment cure rates for both treatment groups were 100% without any tuberculosis-related deaths (20). We examined the safety of levofloxacin use when patients had hepatotoxicity after

Table 1. Overview the selected studies published in English

<table>
<thead>
<tr>
<th>Population</th>
<th>Study design</th>
<th>No. subjects</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Endpoints</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR-TB</td>
<td>Retrospective analysis</td>
<td>99</td>
<td>Levofloxacin + anti-TB drugs (40 patients)</td>
<td>Ofloxacin + anti-TB drugs (59 patients)</td>
<td>Comparison of levofloxacin and ofloxacin in the treatment of MDR-TB</td>
<td>Levofloxacin was more efficacious than ofloxacin when incorporated into multidrug regimens used for MDR-TB</td>
<td>(11)</td>
</tr>
<tr>
<td>Pulmonary TB and HIV(+)</td>
<td>Multi-center RCT</td>
<td>101</td>
<td>Levofloxacin + 4 combined anti-TB drugs (53 patients)</td>
<td>4 combined anti-TB drugs (48 patients)</td>
<td>8 week culture response and effectiveness of 9 months vs. 6 months of intermittent therapy for HIV-related pansusceptible pulmonary TB</td>
<td>Levofloxacin added no benefit to a 4-drug induction regimen. Both 9 and 6 months of intermittent therapy were associated with low treatment failure rates</td>
<td>(18)</td>
</tr>
<tr>
<td>Active TB confirmed by culture</td>
<td>Case-control study</td>
<td>460</td>
<td>Levofloxacin + anti-TB drugs (without INH or RIF) (102 patients)</td>
<td>Anti-TB drugs (with INH and RIF) (358 patients)</td>
<td>Overall rate of major adverse events associated with levofloxacin-containing regimen</td>
<td>Similar rate of adverse events compared with conventional first-line regimens despite a history of adverse events</td>
<td>(20)</td>
</tr>
<tr>
<td>Clinical diagnosis of TB with first-line anti-TB drug-induced hepatotoxicity</td>
<td>Prospective observational study</td>
<td>134</td>
<td>Re-challenge with levofloxacin + EMB ± SM (52 patients)</td>
<td>Re-challenge with EMB ± SM (27 patients)</td>
<td>Safety of using levofloxacin in an endemic area with a high incidence of drug-induced liver injury</td>
<td>Levofloxacin produced no additional hepatotoxicity when used in patients with hepatitis induced by first-line anti-TB drugs</td>
<td>(21)</td>
</tr>
</tbody>
</table>

Abbreviations: MDR = multidrug-resistant, TB = tuberculosis, HIV = human immunodeficiency virus, RCT = randomized controlled trial, INH = isoniazid, RIF = rifampin, EMB = ethambutol, SM = streptomycin.

Table 2. Overview of the selected studies published in Chinese

<table>
<thead>
<tr>
<th>Population</th>
<th>Study design</th>
<th>No. subjects</th>
<th>Treatment</th>
<th>Comparator</th>
<th>Endpoints</th>
<th>Results</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary TB (including re-lapse patients)</td>
<td>RCT according fresh or relapse cases</td>
<td>138</td>
<td>Levofloxacin + anti-TB drugs (different in fresh and relapse cases)</td>
<td>Ofloxacin + anti-TB drugs (different in fresh and relapse cases)</td>
<td>Pharmacokinetics of levofloxacin and the effectiveness and safety in the treatment of pulmonary TB</td>
<td>Levofloxacin 300 mg daily showed the same effectiveness and fewer adverse events in comparison with ofloxacin 600 mg daily</td>
<td>(22)</td>
</tr>
<tr>
<td>Relapse pulmonary TB</td>
<td>RCT</td>
<td>62</td>
<td>Levofloxacin + amikacin or SM, Rifapentin, INH, EMB or Prothionamide (31 patients)</td>
<td>Amikacin or SM, Rifapentin, INH, EMB or Prothionamide (31 patients)</td>
<td>The efficacy and safety of a levofloxacin-containing regimen for the patients with retreatment pulmonary TB</td>
<td>Culture negative rate increased (92.8% vs. 42.8%) after 2 months of treatment, but remained the same after 4 months of treatment</td>
<td>(23)</td>
</tr>
</tbody>
</table>

Abbreviations: TB = tuberculosis, RCT = randomized controlled trial, SM = streptomycin, INH = isoniazid, EMB = ethambutol.

HIV status (23).

Treatment efficacy

Levofloxacin added to a regimen

One study provided no details of HIV status (23).

Levofloxacin was more efficacious than ofloxacin when incorporated into multidrug regimens used for MDR-TB.

Levofloxacin added no benefit to a 4-drug induction regimen. Both 9 and 6 months of intermittent therapy were associated with low treatment failure rates.

Similar rate of adverse events compared with conventional first-line regimens despite a history of adverse events.

Levofloxacin produced no additional hepatotoxicity when used in patients with hepatitis induced by first-line anti-TB drugs.

Abbreviations: MDR = multidrug-resistant, TB = tuberculosis, HIV = human immunodeficiency virus, RCT = randomized controlled trial, INH = isoniazid, RIF = rifampin, EMB = ethambutol, SM = streptomycin.
first-line antituberculosis treatment. In this study, the treatment efficacy was not reported (21).

Comparison of levofloxacin versus ofloxacin added to a regimen
Lu et al. examined the effectiveness and safety of levofloxacin in pulmonary tuberculosis compared with ofloxacin. Levofloxacin, at a dose of 300 mg daily, exhibited the same effectiveness as ofloxacin at a dose of 600 mg daily but with fewer adverse events (22). Yew et al. compared levofloxacin and ofloxacin in the treatment of MDR tuberculosis and the results showed that levofloxacin was more efficacious than ofloxacin when added to multidrug regimens used for treatment of MDR tuberculosis (11).

Adverse events
Levofloxacin added to a regimen
El-Sadr et al. studied HIV-related tuberculosis and found that there was no difference in adverse events between treatment groups with and without levofloxacin. The majority of adverse events in the induction phase were due to hepatic, hematologic or dermatologic reactions and in the continuation phase hepatotoxicity was the major event (18). The trial by Zhao et al. (23) in China reported no difference in the rate of adverse events including epigastralgia, poor appetite, nausea and abnormal liver function test results ($p > 0.05$). However, there were no details about the study and no control groups.

In the case-control study by Marra et al. (20), patients in the levofloxacin arm did not receive concurrent isoniazid or rifampin. The rate of major adverse events was almost halved in those using levofloxacin (rate ratio: 0.60; 95% confidence interval [CI]: 0.44–0.82). After adjustment for the differences of medication, the major adverse event rate was similar for levofloxacin and the control arm (adjusted rate ratio: 0.83; 95% CI: 0.66–1.03). Furthermore, there was no difference between the two arms with respect to CNS (adjusted rate ratio: 0.94; 95% CI: 0.61–1.43), GI tract (adjusted rate ratio: 0.81; 95% CI: 0.58–1.13), skin (adjusted rate ratio: 0.65; 95% CI: 0.38–1.10) or musculoskeletal (adjusted rate ratio: 0.87; 95% CI: 0.48–1.60) related adverse events and hepatotoxicity. Table 3 shows the summary of reported adverse events in six studies.

Our prospective observational trial (21) was designed to examine the risk factors of antituberculosis drug-induced hepatitis and the safety of using levofloxacin/moxifloxacin in tuberculosis patients with DILI caused by antituberculosis treatment. In the levofloxacin group, only four patients developed adverse reactions after treatment: one had dyspepsia, one had a dry mouth, one had diarrhea, and one suffered from dizziness.

Levofloxacin produced no additional hepatotoxicity when used in patients with hepatitis induced by first-line antituberculosis drugs.

Comparison of levofloxacin versus ofloxacin added to a regimen
Lu et al. examined the effectiveness and safety of levofloxacin in pulmonary tuberculosis compared with ofloxacin. Levofloxacin, at a dose of 300 mg daily, exhibited the same effectiveness as ofloxacin at a dose of 600 mg daily but with fewer adverse events (22). Yew et al. compared levofloxacin and ofloxacin in the treatment of MDR tuberculosis and the results showed that levofloxacin was more efficacious than ofloxacin when added to multidrug regimens used for treatment of MDR tuberculosis (11).

Table 3. Summary of reported adverse events in six studies

<table>
<thead>
<tr>
<th>Comparator</th>
<th>Duration of levofloxacin use</th>
<th>Any major event (%)</th>
<th>CNS or PNS major event (%)</th>
<th>GI major event (%)</th>
<th>Skin major event (%)</th>
<th>Hematologic major event (%)</th>
<th>Hepatotoxicity (%)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Levofloxacin vs. ofloxacin</td>
<td>14.6 months vs. 14.1 months</td>
<td>10.0 vs. 11.9; $p &gt; 0.05$</td>
<td>2.5 vs. 6.8 $^a$; $p &gt; 0.05$</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(11)</td>
</tr>
<tr>
<td>Levofloxacin vs. none</td>
<td>8 weeks</td>
<td>12.6 vs. 14.9; $p = 0.83$</td>
<td>1.2 vs. 0.0; $p = 1$</td>
<td>1.2 vs. 0.0; $p = 1$</td>
<td>2.3 vs. 2.3; $p = 1$</td>
<td>3.5 vs. 2.3; $p = 1$</td>
<td>1.2 vs. 5.8; $p = 0.21$</td>
<td>(18)</td>
</tr>
<tr>
<td>Levofloxacin vs. none</td>
<td>186.6 days vs. 108.1 days</td>
<td>29.4 vs. 27.7; $p &gt; 0.05$</td>
<td>11.8 vs. 9.2; $p &gt; 0.05$</td>
<td>16.7 vs. 15.4; $p &gt; 0.05$</td>
<td>4.9 vs. 8.4; $p &gt; 0.05$</td>
<td>NA</td>
<td>8.8 vs. 6.7; $p &gt; 0.05$</td>
<td>(20)</td>
</tr>
<tr>
<td>Levofloxacin vs. none</td>
<td>Variation from 6 days to 9 months</td>
<td>7.7 vs. 3.7; $p &gt; 0.05$</td>
<td>1.9 vs. 0.0; $p &gt; 0.05$</td>
<td>3.8 vs. 0.0; $p &gt; 0.05$</td>
<td>NA</td>
<td>NA</td>
<td>1.9 vs. 3.7; $p &gt; 0.05$</td>
<td>(21)</td>
</tr>
<tr>
<td>Levofloxacin vs. ofloxacin</td>
<td>8 weeks (both groups use levofloxacin in the continuation phase)</td>
<td>15 vs. 19; $p &gt; 0.05$</td>
<td>0.0 vs. 1.4; $p &gt; 0.05$</td>
<td>2.6 vs. 2.9; $p &gt; 0.05$</td>
<td>1.3 vs. 0.0; $p &gt; 0.05$</td>
<td>4.0 vs. 4.3; $p &gt; 0.05$</td>
<td>7.0 vs. 8.0; $p &gt; 0.05$</td>
<td>(22)</td>
</tr>
<tr>
<td>Levofloxacin vs. none</td>
<td>6 months</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>(23)</td>
</tr>
</tbody>
</table>

$^a$ Patients required dosage modification.

Abbreviations: CNS = central nervous system, PNS = peripheral nervous system, GI = gastrointestinal, NA = not applicable.
(13/69) in the ofloxacin arm (p > 0.05); the rate of abnormal liver enzymes was 7% (5/75) in the study arm and 8% (5/69) in the control arm (p > 0.05); the rate of hematologic adverse events was 4.0% (3/75) in the study arm and 4.3% (3/69) in the control arm; the rate of GI tract adverse events was 2.6% (2/75) in the study arm and 2.9% (2/69) in the control arm; the rate of CNS adverse events was 0% in the study arm and 1.4% (1/69) in the control arm; the rate of skin adverse events was 1.3% (1/75) in the study arm and 0% in the control arm.

In the study by Yew et al. carried out in Hong Kong, the rate of adverse events for levofloxacin was similar to that of ofloxacin (10.0% vs. 11.9%; p > 0.05). A reduction in the dose of levofloxacin was required in only one patient while dose modification or substitution of ofloxacin was required in four patients. There were no details about adverse events in different organ systems (11).

Discussion

In vitro, levofloxacin has been proved to be active against M. tuberculosis (26–29). It has been used in MDR tuberculosis patients or those intolerant of first-line antituberculosis treatment like other newer fluoroquinolones (9, 30). The objective of this review was to identify and summarize the safety data pertaining to the use of levofloxacin for the treatment of tuberculosis. Although most other studies examined the efficacy of levofloxacin in tuberculosis treatment (31–32), only six reports included in this review were clinical studies involving the recording of the rates of adverse events. The results of the four trials with added levofloxacin and two trials comparing levofloxacin and ofloxacin show that it is safe to use levofloxacin in patients with tuberculosis.

Marra et al. (20) focused on the safety of levofloxacin in antituberculosis treatment. This study compared a levofloxacin-containing regimen with conventional first-line regimens and a similar rate of adverse events was reported. However, this was just a case-control study. Two randomized controlled trials (written in Chinese) compared levofloxacin added to a regimen with conventional antituberculosis regimens and one randomized controlled trial (written in Chinese) compared levofloxacin with ofloxacin. However, the number of patients in the study groups of these three trials was always less than 80 (18, 22, 23). A large randomized controlled trial is necessary to determine the efficacy and safety of levofloxacin in patients with tuberculosis.

Fluoroquinolones have also been as prophylaxis in patients exposed to MDR tuberculosis (8). Two reports described the inability to tolerate levofloxacin combined with pyrazinamide in the prophylaxis of latent MDR tuberculosis (33, 34). Papastavros et al. described 14 of 17 individuals (about 82%) who were treated with pyrazinamide and levofloxacin who experienced at least one adverse event and 8 patients (47%) with elevated liver enzymes (33). Lou et al. evaluated the long-term tolerability of pyrazinamide and levofloxacin in patients exposed to MDR tuberculosis after solid organ transplantation. Twenty-seven (56.3%) of the 48 patients discontinued therapy within four months due to adverse events (34). GI intolerance was the major adverse event for early discontinuation. The reason for the unacceptable high ratio of adverse events associated with the combination of pyrazinamide and levofloxacin is still unknown. Drug-drug interactions or specific patient population in one study (33) may have contributed to the result. However, in the six studies included in this review, El-Sadr et al. (18) and Lu et al. (22) added levofloxacin to antituberculosis drugs, including pyrazinamide, in the study group during the first two months. There were no additional adverse events reported in the study group. In the case-control study reported by Marra et al. (20), patients in the levofloxacin group containing pyrazinamide had fewer adverse events than in the control group (52% vs. 92%). There were also no additional adverse events, possibly due to fewer patients being given pyrazinamide.

Intolerance to first-line antituberculosis drugs, including drug-induced hepatotoxicity, is one indication for the use of fluoroquinolones in tuberculosis treatment (13). Although fluoroquinolones may induce mild elevation of liver function enzymes, they carry no additional risk of hepatotoxicity for tuberculosis patients in previous studies (4, 17). Ofloxacin use in patients with pre-existing chronic liver disease or hepatotoxicity is safe (35, 36). In the previous study (13), levofloxacin was used in the patients who developed hepatotoxicity after first-line antituberculosis treatment. Because of the high incidence of antituberculosis drug-induced hepatotoxicity and the longer time needed to achieve liver function normalization, new and less hepatotoxic regimens may be needed before a challenge with first-line antituberculosis drugs. Such a regimen might include streptomycin, ethambutol, a fluoroquinolone, or another second-line oral drug. In this study, we found that levofloxacin and moxifloxacin produced no additional hepatotoxicity in patients following first-line antituberculosis therapy. These two drugs could be safely prescribed while waiting for liver functions to return.
to normal. No drug-induced hepatitis was found in these patients during the follow-up. Levofloxacin was found to be safe during long-term use (21).

Conclusions
Levofloxacin has been shown to be safe for use in tuberculosis treatment in the studies described in this review. It is also safe when used in patients who developed hepatotoxicity after first-line antituberculosis drugs. Because of the high degree of variability in study design, it is difficult to reach a general conclusion about all the studies. There were only three small randomized controlled studies of levofloxacin use in pulmonary tuberculosis. More research is needed to confirm the efficacy and safety of levofloxacin in tuberculosis treatment.

REFERENCES

Safety of Levofloxacin in Tuberculosis Treatment


