Clinical use of Levofloxacin in the long term treatment of drug resistant tuberculosis

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Clinical use of Levofloxacin in the long term treatment of drug resistant tuberculosis

L. Richeldi, M. Covi, G. Ferrara, F. Franco, P. Vailati, E. Meschiari, L.M. Fabbri, G.Velluti

ABSTRACT: ***Clinical use of Levofloxacin in the long term treatment of drug resistant tuberculosis. L. Richeldi, M. Covi, G. Ferrara, F. Franco, P. Vailati, E. Meschiari, L.M. Fabbri, G.Velluti.***

Multidrug-resistant (MDR) tuberculosis (TB) is a form of TB that is resistant to some of the first-line drugs used for the treatment of the disease. It is associated both with a higher incidence of treatment failures and of disease recurrence, as well as with higher mortality than forms of TB sensitive to first-line drugs. Levofloxacin (LFX) represents one of the few second-line drugs recently introduced in the therapeutic regimens for MDR TB. We report our experience concerning *in vitro* activity and clinical safety of LFX in long term second-line regimens for MDR TB.

***In vitro* activity on Mycobacteria: The *in vitro* activity of ciprofloxacin, ofloxacin and LFX was studied on 28 strains belonging to different species of *Mycobacteria*. In Dubos medium, LFX inhibited the growth of both library and MDR clinical *Mycobacteria* strains in a range of 0.25-1 mcg/ml. In International Union Tuberculosis Medium (IUTM) the minimum inhibitory concentrations (MIC) were slightly higher, but LFX activity was not affected by the higher complexity of the medium.**

Clinical Experience: Four patients with MDR TB were treated with a second-line regimen comprising oral LFX 500 mg twice daily, for at least 9 months. Two isolates obtained from the patients reported here showed multi resistance to isoniazid and rifampin, one to rifampin and streptomycin and one to isoniazid and ethambutol. During therapy, no significant alteration of either liver function tests, blood tests or any other described side effect of the fluoroquinolone class was observed. The 3 patients with pulmonary MDR TB showed radiologic and clinical improvement.

Conclusion: We confirm the higher *in vitro* activity of LFX compared to older fluoroquinolones. Furthermore, in a limited number of MDR TB patients, second-line regimens comprising LFX 500 mg b.i.d. administered in a range of 9-24 months were well tolerated and safe.
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***Keywords:* Tuberculosis, multidrug-resistant, levofloxacin, long term.**

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Multidrug-resistant tuberculosis (MDR TB) is a form of TB that is resistant to the first-line drugs [at least rifampin (RAMP) and isoniazid (INH)] recommended for the treatment of the disease (table 1). When compared to TB, MDR TB is associated with both higher incidence of treatment failures and disease recurrence, as well as with higher mortality [1]. Thus, in the case of MDR TB second-line drugs must be introduced, although they may present disadvantages in terms of effectiveness, side effects and costs [2].

Standardized therapeutic guidelines for MDR TB have yet to be developed. Thus, treatment regimens are individualized on the basis of: i) the patient's clinical history, ii) antibiogram (when available), and iii) the physician's experience. World Health Organization (WHO) guidelines recommend regimens consisting of at least 3 drugs, preferably 4 or 5, not previously administered to the patient, of proven sensitivity, for at least 18

Table 1. – First and second-line drugs for the treatment of multidrug-resistant tuberculosis (MDR TB)

First-line drugs	Second-line drugs
Isoniazid	Amikacin/Kanamycin
Rifampin	Capreomycin
Ethambutol	O-/Cipro-/Levo-/Moxi-floxacin
Pyrazinamide	Ethionamide
Streptomycin	Clofazimine
	Cycloserine/Terizidone
	Aminosalicilic acid
	Rifabutin
	Amoxycillin/Clavulanic acid

Modified from: [3].

months after sputum conversion. Treatment administration should be directly observed (Directly Observed Therapy, DOT) [3]. Many studies have shown the *in vitro* and *in vivo* activity of fluoroquinolones against *Mycobacterium tuberculosis* [4–10]. Thus, their use as second-line treatment of MDR TB has been recommended by the WHO [2, 3, 11]. Levofloxacin (LFX) is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin and it has recently become available for therapy (1993 in USA, 1998 in Italy). The mechanism of action relies on the DNA-DNA-gyrase complex by inhibiting DNA gyrase (topoisomerase II) mainly in Gram-negative bacteria, and topoisomerase IV mainly in Gram-positive bacteria, but no studies on the LFX molecular target in Mycobacteria have been published [12]. LFX is the first long half-life (>7 hours) fluoroquinolone available for clinical use at a once daily schedule, moxifloxacin being only recently released in Italy while gatifloxacin is expected in the next few years. In terms of pharmacodynamics, the clinical efficacy of LFX in community-acquired infections has been shown to be predicted by the ratio of the area under the curve (AUC) to the minimum inhibitory concentrations (MIC), or by the maximum plasma concentration (Cmax)/MIC ratio [13]. Amongst these drugs, LFX has the largest documented tolerability in terms of treated patients [14–16].

After the international clinical development program, LFX has shown good tolerability. Undesired side effects included those already reported either for fluoroquinolones or other antibiotics (i.e. nausea, diarrhea, headache) [16]. In particular, there was not a statistically significant incidence of either cardiovascular (prolonged Q-T, torsade de pointe) or hepatic/pancreatic events. Furthermore, post marketing surveillance has shown for LFX a very good safety profile: in particular, undesired events (pathologic manifestations that do not depend directly on the cause-effect relationship with the drug) are very rare (<0.01%) (table 2) [15].

The aim of this study was to retrospectively evaluate the clinical use of LFX in long term therapies in association with other first- and second-line anti-TB drugs in patients with MDR TB or TB caused by RAMP-resistant strains.

Table 2. – Incidence rates of minor levofloxacin (LFX) undesired events

Number of patients exposed to LFX: 2.000.000
Number of reported events: 193 (Incidence <0.01%)

Affected organ/apparatus	N	%
Aspecific	40	21
Skin	37	19
Central nervous system (CNS)	35	18.5
Muscles/Tendons	35	17.5
Digestive	21	11
Respiratory	15	8
Cardiovascular	10	5
Total	193	100

Modified from: [15].

In vitro activity on *M. Tuberculosis*

Before introducing LFX into the treatment of TB, some *in vitro* experiments on Mycobacteria were carried out at our Institution. The *in vitro* activity of ciprofloxacin, ofloxacin and LFX was evaluated on: 2 strains from a human library and 18 clinical isolates of *M. tuberculosis*; 8 strains of *Mycobacterium avium* complex (MAC); and 2 *Mycobacterium bovis* strains. The activity of the 3 antimicrobial agents was assayed in Dubos broth and in the agar medium, International Union Tuberculosis Medium (IUTM). Controls (i.e. tests without drugs) were also introduced. Mycobacteria inocula were set by turbidimetry to <100 Colony Forming Units (CFU). The strains that showed a 5-10% growth with respect to the controls were considered resistant to the specific concentration of fluoroquinolone tested.

In the broth medium, LFX inhibited the growth of all the *M. tuberculosis* strains in a concentration range of 0.25-1 mcg/ml. In IUTM, MIC values were slightly higher. However, 2 strains of MDR *M. tuberculosis* were inhibited by LFX concentrations of 0.5 and 1 mcg/ml, respectively. Ciprofloxacin and ofloxacin did not inhibit any strain below the concentration of 1 mcg/ml: 10 *M. tuberculosis* strains were inhibited in a range of 1-5 mcg/ml, the remaining strains being resistant also to concentrations above 5 mcg/ml. All MAC and *M. bovis* isolates were resistant to the 3 study drugs, up to a concentration of 10 mcg/ml.

Clinical experience

To evaluate tolerability and safety of LFX in long term (more than 3 months) second-line regimens, we retrospectively reviewed clinical, radiologic and laboratory data of 4 patients treated at our Institution between December 1999 and September 2000 for MDR TB. A description of each case follows.

Patient 1: 41-year-old Caucasian female, no concomitant disease. In her past medical history she reported having been treated in 1991 and 1995 with standard treatment for cavitary pulmonary bacilliferous TB with severe fibrocavitary sequelae in both lung upper lobes. In both episodes the patient voluntarily quitted treatment, at 3 and 5 months respectively. Following the occurrence of persistent dry cough, high resolution computed tomography (HRCT) of the chest was performed, which showed a “tree-in-bud” image (figure 1). After fiberoptic bronchoscopy, the microscopic examination of the bronchial exudate was negative for acid fast bacilli (AFB), whereas the molecular test (LCx® method, Abbott Diagnostics, US) resulted positive. The patient was initially treated with LFX (500 mg twice a day), INH (300 mg once a day), pyrazinamide (PZA) (1200 mg once a day), ethambutol (ETB) (1200 mg once a day) and

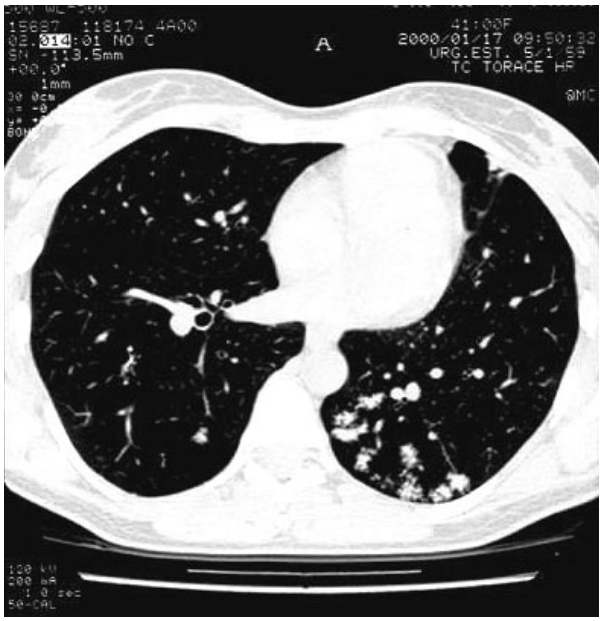

Fig. 1. – High resolution computed tomography (HRCT) scan of patient 1 at the beginning of treatment with LFX, showing a "tree-in-bud" appearance.

rifabutin (RBT) (300 mg once a day). The susceptibility test for *M. tuberculosis* showed ETB and INH resistance. Thus, the therapy was modified as follows: LFX (500 mg twice a day), PZA (1200 mg once a day), INH (300 mg once a day), RBT (300 mg once a day) and clofazimine (CLF) (100 mg once a day). This regimen was then continued for 12 months. At the end of the treatment period, the patient had improved both clinically and radiologically.

Patient 2: 39-year-old Caucasian male, no concomitant disease. In 1999, the patient was treated with a standard 5-drug regimen for cavitary pulmonary TB of both upper lobes with severe fibrocavitary sequelae. One year after completing treatment, following the reappearance of asthenia, fever and cough with purulent expectoration, the patient was readmitted with the diagnosis of pulmonary bacilliferous TB relapse. The following regimen was introduced: LFX (500 mg twice a day), ETB (1500 mg once a day), PZA (1500 mg once a day), INH (300 mg once a day) and CLF (100 mg once a day). Susceptibility test on *M. tuberculosis* isolate revealed RAMP and streptomycin (STM) resistance. After 3 months of treatment and sputum conversion, the patient was discharged and continued the initial regimen for a further 6 months. Thereafter, he continued the treatment with INH, ETB and PZA for 6 months. The clinical picture showed improvement but radiological findings remained unchanged.

Patient 3: 77-year-old Caucasian female, affected by herpetic neuritis of the right eye. At the time of admission the patient was on full-dosage RAMP-INH-ETB regimen for genitourinary TB. Despite therapy, the general conditions and blood chemistry tests worsened. The *M. tuberculosis* strain obtained from a urinary specimen revealed RAMP and INH resistance. Due to a variety of drug intolerances, a 2-drug regimen with LFX (500 mg twice a day) and terizidone (TZD) (250 mg three times a day) was adopted. Therapy led to an improvement of the patient's clinical condition and to stabilization of the radiological and functional findings. However, the urine specimens were persistently positive for *M. tuberculosis* after 2 years of treatment.

Patient 4: 65-year-old Caucasian male, affected by chronic respiratory failure (treated with long term oxygen therapy), type 2 diabetes, bilateral arthrosis of the hip and chronic liver disease due to alcohol. Five months before admission, the patient had been treated with a standard 5-drug regimen for pulmonary bacilliferous TB. The patient voluntarily stopped treatment after 2 months. He was admitted to our Clinic following the reoccurrence of cough with purulent expectoration, low grade fever and asthenia. Radiographic evaluation showed a cavity in the apical segment of the left lower lobe. Direct examination of sputum showed AFB. The patient was initially treated with full-dose RAMP, INH, ETB, PZA and ofloxacin. However, after the first month of treatment, the clinical and radiological findings were still unchanged. The drug susceptibility test confirmed the clinical suspect of RAMP and INH resistance. Thus, a regimen with LFX (500 mg twice a day), ETB (1500 mg once a day), INH (300 mg once a day), PZA (1500 mg once a day), CLF (100 mg once a day) was adopted, yielding to an improvement in the clinical conditions. The radiologic findings slowly improved, as documented by a series of chest HRCT scans (figure 2). Cultural examinations for *M. tuberculosis* converted to negative after 12 months, whereas all other microbiologic exams remained persistently positive. Anti-TB therapy was continued for a total of 12 months.

Safety and tolerability evaluation results

Laboratory test review did not reveal any significant alteration in any of the patients. In particular, liver function tests [bilirubin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transpeptidase (γ-GT)] did not increase beyond 3 times normal values, even though other potentially hepatotoxic drugs were included in the association therapy. Hematopoiesis indexes did not show any alteration. No side effect described for the LFX pharmacological class was observed, including gastrointestinal (diarrhea), cardiovascular (rhythm alteration) and skeletal muscle (tendon breakage) side effects. Patient 4 experienced two epilepsy-like seizures which could not be explained otherwise and did not require modification of therapy since the electroencephalogram (EEG) and the brain computed tomography (CT) scan performed out after the episodes did not show any alteration. The same patient repeatedly complained of gonalgia, which was probably due to a pre-existent arthrosis of the knee and to hyperuricemia secondary to pyrazinamide therapy. Patient 2 complained of headache during the first month of treatment. However, he had previously shown an anx-

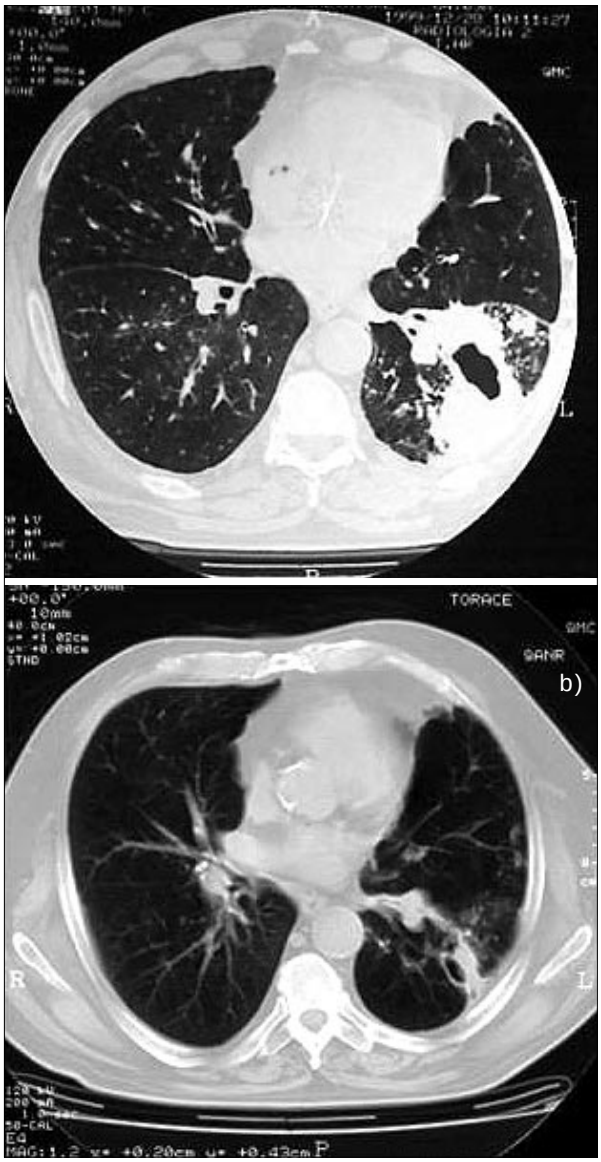

Fig. 2. – HRCT scan of patient 4 before (panel A) and after (panel B) treatment including LFX, showing the improvement of the cavitary lesion in the apical segment of the lower left lobe after 15 months of second-line anti-TB therapy.

ious personality. All 3 patients affected by pulmonary TB showed radiologic and clinical improvement of the lesions during treatment.

Discussion

MDR TB is a form of TB that is resistant to the first-line drugs (at least RAMP and INH) used for the treatment of the disease. When compared to forms of TB that are sensitive to first-line drugs, MDR TB is associated with a higher incidence both of treatment failures and of disease recurrence, as well as with higher mortality [2]. The increasing prevalence of MDR TB, especially in developing countries, highlights the need for new treatment strategies including second-line drug regimens in the DOT strategy (the so-called "DOTS plus") [17, 18]. Despite research efforts regarding new therapeutic agents active against resistant *M. tuberculosis* strains, fluoroquinolones are the only new antimicrobial agents introduced in the last 20 years in anti-TB regimens and evidence of their clinical efficacy is increasing [19, 20].

We report here our experience on *in vitro* activity and clinical use of LFX. LFX showed a 2-4 times higher *in vitro* activity against resistant and MDR *M. tuberculosis* strains with respect to ciprofloxacin and ofloxacin, both in broth and agar media, in accordance with available published data [21]. No activity was shown against MAC strains. However, it should be remembered that the *in vitro* testing of *Mycobacteria* is far from being standardized and that high intra- and extra-laboratory variability is to be expected. Thus, more accurate and reproducible results will be available when a general consensus on the *Mycobacteria in vitro* assay is reached.

We retrospectively reviewed the LFX safety and tolerability in 4 patients treated over a period of 9-24 months with second-line regimens comprising LFX 500 mg twice a day. The reason for the higher LFX daily dose was to address the pharmacodynamic properties of the drug. The clinical efficacy of LFX has been shown to be predicted by the AUC/MIC or Cmax/MIC ratios [13]. Anecdotic reports are available on the efficacy of LFX in the treatment of TB, but no data on MDR TB LFX therapy could be found. To raise the expected clinical efficacy of LFX, we decided to increase the daily AUC/MIC ratio, the drug's Cmax being already elevated (5.7 mg/L in healthy subjects) [14] and the toxic effect of fluoroquinolones being concentration dependent [16]. Furthermore, shorter courses of LFX 500 mg b.i.d. in severe infections have been published [22].

Laboratory tests failed to show any significant alteration, especially in liver function tests (bilirubin, AST, ALT, alkaline phosphatase, γ-GT) and red blood cells and platelets counts. No adverse effect typical of the LFX pharmacological class was observed. Patient 4 experienced two epilepsy-like seizures which could not be explained otherwise and did not require discontinuation of the drug. Patient 2 complained of headache during the first month of treatment.

Overall, we confirm the higher *in vitro* activity of LFX compared to older fluoroquinolones. Furthermore, in a limited number of MDR TB patients, second-line regimens comprising LFX 500 mg b.i.d. administered in a range of 9-24 months were well tolerated and safe.

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