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Optimizing levofloxacin dose in the treatment of multidrug-resistant tuberculosis

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General introduction and scope of thesis



TB today and current research goals

Tuberculosis (TB) is an infectious disease caused by *Mycobacterium tuberculosis* (*Mtb*). It causes more deaths worldwide than any other infectious disease (1). In 2017, an estimated 10 million (range, 9.0–11.1 million) people developed TB and 1.3 million (range, 1.2–1.4 million) died from TB (1). Multi-drug resistant TB (MDR-TB), a form where the infecting strain is resistant to two important first line drugs (isoniazid and rifampicin) have threatened global TB control and elimination efforts. The incidence of MDR-TB is around 3.5 % in new TB cases and 18 % in previously treated cases whereas the treatment success rate is only 55 % in studies — and under service conditions, even lower (1). This high death toll is a man-made disaster: with timely diagnosis and proper care, the majority of people developing TB can actually be cured. Worldwide, the average rate of decline in TB incidence remained only at 1.5 % per year from 2000–2017 and 1.8 % between 2016–2017. An accelerated annual decline of 4–5 % is needed by 2020 and to 10 % per year by 2025 to achieve the milestones of the end TB strategy (1, 2). TB primarily affects the lungs but also can cause disease in other organs such as bone, eye, lymph nodes, brain, digestive tract, peritoneal and pleural cavities, and the urogenital tract. In humans, TB is spread by airborne droplets originating from a contagious individual while coughing or sneezing (3). Immediately after infection, the bacterium is able to survive within macrophages. More than 90 % of all infected individuals either overcome the infection by intra-cellular killing or remain in a lifelong latent stage by immunity-mediated capsulation of the mycobacteria within granulomas. Around 5–10 % of infected people develop active disease during their lifetime, especially when the immune system is compromised — and half of these typically develop TB within the first two years after infection (4).

Historical background

Tuberculosis (TB) is an old disease that has ravaged humans since centuries. No other disease in the history of mankind has caused the extent of morbidity and mortality as TB. Thought to be as old as humanity itself, the TB bacteria originated parallel to the evolution of *Homo sapiens* in Africa more than 70,000 years ago and spread out of continent following human migrations (5, 6). The cause remained unknown until 1882 when

the German microbiologist Robert Koch reported the successful isolation of the causative agent of TB. A year later, the bacillus was named *Mycobacterium tuberculosis* (*Mtb*) (7). *Mtb* is an acid-fast bacillus that grows slowly with a doubling time of 12–24 h. The peculiar cell wall structure of *Mtb* that contains peptidoglycan and complex lipids, plays a major role in its virulence. The cell wall structure also prevents the penetration of drugs. During active disease, most bacilli are in a metabolically active state with replication times around 24 h; this phenotype is vulnerable to antimicrobial drugs some of which have bactericidal capacity (6). Under stress conditions, a specific genetic program is switched on, called dosR regulon — driven by a set of 48 genes resulting in persistent infection (8). Curative treatment requires long-term exposure to specific drugs with so-called sterilizing capacity in order to eradicate these persistence-phenotype organisms (9). Taken together, to target the different metabolic states of *Mtb* adds to the difficulty to treat TB effectively (6).

Early medical drug development and drug resistance

This discovery of *Mtb* was also the beginning of a trend to its control. The modern era of effective TB treatment started in the mid-1940s after the discovery of streptomycin. However, soon after its use in TB patients, it became clear that although patients improved dramatically in the beginning, most of them ended up selecting resistant sub-population to streptomycin. This led to a new understanding of two requisites of an effective TB care: treatment with multiple antibiotics — to cover resistant mutants present in the microbial population; and long-lasting therapy, to ensure complete eradication of persistent organisms by sterilizing all affected body sites (10). As stated earlier, two factors need to be considered. First, it is the genotypic resistance in a sub-population of *Mtb*. Infecting TB bacteria may comprise both susceptible and genetically resistant strains. With every cell division, there is a chance that point mutations occur. For the development of resistance to INH, an estimated 1 in 10^8 – 10^9 cell divisions may result in a drug-resistant mutant; *inhA* and *katG* genes are the relevant genes that code for INH susceptibility. Rifampicin resistance is coded for by mutations in the *rpo-B* gene. The higher the bacterial burden, the higher is the chance of the emergence of a resistant sub-population (11). Monotherapy allows

the selection of these resistant mutants by creating a selective pressure leading to repopulation with the resistant mutants, ultimately resulting in therapy failure (6). Treatment with multiple drugs makes it less likely for a resistant mutant to survive, as these mutant strains will not survive even if the effective drug is only a bacteriostatic companion drug (6). Second, the phenotypic tolerance to administered antibiotics that gives rise to persisters. In humans, *Mtb* exists in different metabolic phases: a logarithmic-growth-phase, a slowly replicating acid-phase-growth and a non-replicating-persister-phase (12). These persisters may be seen in patients who relapsed early because of a sub-population of non-replicating bacteria that survived until the end of treatment and left the non-replicating phase after the treatment was over. In this case, the bacteria may be still susceptible to the initial antibiotics without any changes in the nucleic acid sequence of its genome. Therefore, treatment for a longer period will give enough time to kill the bacteria at non-replicating or slow replicating phase as they periodically enter the replicating phase during treatment.

Between 1950 and 1960, the most effective four-drug treatment regimen to cure drug-susceptible tuberculosis (DS-TB) was developed and finally tested in large randomized trials between 1970s–80s initiated by British Medical Research Council (13–16). This included isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) (13–16). In particular, the introduction of rifampicin, in 1960, was considered a major breakthrough because it reduced the treatment duration from eighteen months to nine months due to its sterilizing ability.

Although discovered in 1950s, re-introduction of low dose pyrazinamide (20–25 mg/kg) in 1970s –enabled the formation of the current ‘short-term’ treatment regimen of six months as it accelerated the sterilizing effect of rifampicin (13, 15, 16). Although, the trials from 1970 used 35–40 mg/kg dosing, however, in programmatic settings 20–25 mg/kg dose was chosen, which seems sub-optimal (17).

The turn of 20th century was marked by social and economic development in Western Europe, North America and some other parts of the world. As a result, the incidence and deaths related to TB slowly started to decline due to improvement in incomes, housing, nutrition and strong political commitment. From 1950s–60s, national case rates fell by up to 10 % per year and death rates plummeted. These countries

now have only 10 or fewer cases per 100,000 inhabitants which made TB a forgotten disease (18). But for many low- and middle-income countries “TB did not go away and is still inflicting morbidity and deaths” (1).

In 1993, TB was declared a global health emergency by the WHO (19). To fight efficiently against this global epidemic, Directly Observed Treatment, Short Course (DOTS) was introduced as a TB control strategy (18). The DOTS strategy focused on the treatment of new drug-susceptible TB cases with standardized regimen with first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol). Compared with a 41 % cure rate of other treatment programs, DOTS achieved a 77 % cure rate (4) in programmatic settings and was hailed as important milestone in TB control. It was hoped that the global TB epidemic could be controlled by the beginning of 21st century. Alarmingly in 1997, the global drug resistance survey conducted by the WHO reported multi-drug resistant TB (MDR-TB) on a global scale for the first time. MDR-TB is defined as resistance of the infecting bacteria to two most powerful first line drugs namely isoniazid and rifampicin. As a response, “DOTS plus strategy” was developed for the programmatic management of MDR-TB in 1999. The DOTS plus strategy included three important pillars: diagnosis based on culture, individual drug susceptibility testing of Mtb isolates and use of first- and second-line drugs in the treatment of MDR-TB. Furthermore, to increase the access to second-line drugs and to prevent the development of acquired-drug resistance, the WHO and Stop TB partnership have been supporting low- and middle-income countries to procure drugs at highly concessionary prices (60–90 % price reductions) through the Green Light Committee (GLC) initiative (18). Despite the efforts, the rise of drug resistant strains necessitates development and optimization of new combinations for the treatment of drug-resistant TB.

Bedaquiline and delamanid are two examples of recent drug developments. In 2012, bedaquiline was approved by the U.S. Food and Drug Administration while delamanid has received conditional regulatory approval based on Phase IIb trial results in 2014. At present, there are 11 new compounds and 12 vaccines in phase I, II or III trials (1).

Treatment of MDR-TB

There are two standardized regimens in use to treat MDR-TB: a short 9-month and a long 20-month regimen. In August 2018, the WHO

endorsed a fully oral 20-month regimen for MDR-TB (Table 1) replacing the older 20-month regimen containing injectable agents. The new classification was based on the latest evidence on effectiveness and safety of the drugs recommended in Table 1, derived from individual patient data from clinical trials, cohort/observational studies, along with treatment outcomes results (20). Furthermore, the drugs in the new regimen were chosen taking into account several considerations: preference of oral above injectable agents, the results of drug susceptibility testing (DST), the reliability of existing DST methods, population drug resistance levels, history of previous use of medicine in individual patients, drug tolerability and potential drug-drug interactions (21) .

In May 2016, the shorter 9-month MDR-TB regimen was conditionally recommended in patients if eligible. The regimen comprises of seven drugs (moxifloxacin, kanamycin, prothionamide, clofazimine, pyrazinamide, high-dose isoniazid, and ethambutol) in the intensive

Table 1: Classification of drugs for use in longer MDR-TB regimen (21)

Group	Medicine
Group A (Priority drugs)	Levofloxacin (Lfx) OR Moxifloxacin (Mfx)
	Bedaquiline (Bdq)
	Linezolid (Lzd)
Group B (Add on drugs)	Clofazimine (Cfz)
	Cycloserine (Cs) OR Terizidone (Trd)
Group C (When Group A and B drugs cannot be used)	Ethambutol (E)
	Delamanid (Dlm)
	Pyrazinamide (Z)
	Imipenem-cilastatin (Imp-Cln) OR Meropenem (Mpm)
	Amikacin (Am) OR [Streptomycin (S)]
	Ethionamide (Eto) OR Prothionamide (Pto)
	p-aminosalicylic acid (PAS)

phase of 4–6 months and four drugs (moxifloxacin, clofazimine, pyrazinamide and ethambutol) in the continuation phase of 5 months. The regimen had excellent treatment outcomes in multi-center trials around the globe: Bangladesh (84.4%), Cameroon (89%), Niger (89.2%) and other African countries (22–24). This is the only evidence-based regimen to treat MDR-TB. However, the only draw-back of the shorter regimen is ineligibility of patients, especially in the settings where resistance to second-line drugs is high (25). In European Union (EU) and European Economic Area (EEA) region, only 11% of the rifampicin resistant or MDR-TB were eligible for the shorter regimen (26–28).

Recent findings from the Stream Stage I trial that compared the shorter vs the longer regimen in programmatic settings in Ethiopia, South Africa, Vietnam and Mongolia revealed that there is a little difference between two treatment arms in terms of overall frequency of severe (grade 3–5) adverse events (48.2% on the shorter vs 45.4% on the longer regimen). There was more QT prolongation in the shorter regimen with twice as many participants having $QT/QTcF \geq 500$ ms, occurring at any one time point during the treatment. However, QT prolongation was effectively managed by regular ECGs and reduction of the moxifloxacin dose to 400 mg daily. Alanine transaminase abnormalities were more common in the shorter regimen at 8 weeks but this did not translate into clinically important hepatic events (Stream I trial results, 49th UNION World Conference, 27th October 2018). Moreover, the shorter regimen showed an overall comparable likelihood of treatment success with longer regimens, with a lower risk of treatment interruption. In addition, the shorter regimen resulted in reduced health care costs per patient (around 16.7% reduction in cost per patient South Africa [\$1,784] and 27.5% reduction in Ethiopia [\$1,628]). However, shorter regimens were associated with higher risks of treatment failure and relapse compared to longer regimens, especially when resistance to key medicines in the shorter regimen was present (21). This warrants careful selection of patients eligible for shorter regimen based on DST results.

Fluoroquinolones and Therapeutic drug monitoring

Fluoroquinolones (FQs, levofloxacin and moxifloxacin) play a pivotal role in the treatment of MDR-TB (29). FQs work by inhibiting DNA gyrases and therefore, preventing bacterial DNA synthesis, and display

excellent *in vitro* and *in vivo* activity against *Mtb* (30). Minimum inhibitory concentrations are low in both laboratory and clinical isolates from TB patients. Moreover, FQs display excellent early and extended bactericidal activity during first two weeks of treatment (29,31–34).

Lfx was first marketed in 1993 in Japan to treat infections caused by both gram-positive and gram-negative bacilli. Later in 2001, its use was repurposed in TB, after a Chinese study proved the strong *in vitro* and *in vivo* efficacy against *Mtb* (35). Since then, it has been considered an important agent and firmly holds its position as a Class A agent against MDR-TB (21). In general, Lfx is well tolerated and has a good safety profile in long-term use, although it does have potential to cause side-effects involving tendons, muscles, nerves, joints and the central nervous system (36). Lfx is currently prescribed at 750–1000 mg once daily for adult patients (21). However, this dose has resulted in substantial variability in serum/plasma concentrations, and therefore in efficacy, since its activity is concentration dependent (32–34,37,38). Acquired FQs resistance during standard treatment resulting in poor outcomes as shown in a prospective observational cohort study has become a serious concern (24). An earlier study by the same group showed that 11.2 % (79/832) of MDR-TB patients developed FQ resistance without any baseline resistance (39,40). Several mechanisms have been identified for the development of this functional drug resistance. The most important factor is sub-optimal drug exposure achieved in patients with FQs based regimens, due to inadequate dosing and/or poor adherence to the treatment (41). Furthermore, sub-optimal drug concentrations on the same standardized dosing could be a result of large inter- and intra-individual variabilities among TB patients (32,34).

Therapeutic drug monitoring (TDM) is a useful tool that helps clinicians make informed dosing decision. By measuring the plasma/serum concentrations of a given drug, the dose can be increased if sub-therapeutic concentrations are reached; and decreased, if toxic. It is important to strike the balance that is based on maximizing efficacy and minimizing toxicity. TDM guided dosing is a routine procedure in some TB centers around the world (42,43). As a result, the treatment centers in the Netherlands and Sweden have shown excellent treatment success rates between 77–86 % for MDR-TB, while global average is staggering at 55 % (1,42,43). The importance of TDM in the

management of patient's sub-groups of drug-susceptible TB (if drug malabsorption or under dosing was suspected) was first introduced in the clinical practical guidelines by the American Thoracic Society, Centers for Disease Control and Prevention and, Infectious Diseases Society of America and was endorsed by the European Respiratory Society and the US National Tuberculosis Controllers association (44). Although widely acknowledged, TDM still seems farfetched in programmatic settings of TB endemic countries. Despite high reliability and accuracy, conventional TDM using plasma/serum is challenging in low-resource settings. The invasive nature of sampling, need of skilled personnel for venipuncture, potential infectious hazard with blood sampling, cooling requirements for transportation and storage, need for advanced analytical equipment, and high costs makes TDM using venous sampling difficult (45). Moreover, the estimation of a full area under concentration time curve (AUC_{0-24}) which requires at least 10–12 blood samples at different-time points is burdensome to TB patients. Therefore, limited sampling strategies that utilize two to four time-points for AUC_{0-24} estimation (46) and alternative stress-free sampling strategies using saliva or capillary blood through a fingerpick and dried blood spots cards, for drug concentrations measurement might be the future of global TDM, that could actually be implemented today (47,48).

AIM OF THE THESIS

The overall aim of this thesis is to understand the pharmacokinetics of Lfx in MDR-TB patients and its possible relation to optimize TB treatment. This thesis strives to find answers to the following clinical questions:

1. Is there a role of pharmacokinetic/pharmacodynamic (PK/PD) approaches in treatment optimization of Lfx? What should be the PK/PD target?
2. Based on that target, can we use TDM to find the right dose?
3. How feasible is TDM in resource limited settings using conventional venous sampling? Can TDM be accomplished using alternative sampling strategies such as saliva?

4. What is the optimal daily dose and dosing frequency of Lfx under programmatic conditions, to serve the majority of patients?

OUTLINE OF THE THESIS

In **Chapter 2**, we will review the available literature on Lfx use in MDR-TB treatment. Our aim here is to evaluate the efficacy of Lfx dosing by integrating the pharmacokinetic/pharmacodynamic (PK/PD) parameters. For pharmacokinetic variability, studies with a prospective, observational or retrospective design in TB patients were included. MIC data were retrieved from *in vitro* studies on susceptibility of *Mtb* strains to Lfx.

In **Chapter 3**, we propose tools and strategies for implementing TDM alongside the WHO list of essential *in vitro* TB diagnostics.

In **Chapter 4**, a retrospective study will be performed to evaluate the influence of co-variates on treatment outcomes of MDR-TB patients on Lfx containing standardized regimens in Nepal.

In **Chapter 5a**, the development and validation of a novel method to analyze Lfx and its metabolite in human plasma using liquid chromatography- tandem mass spectrometry is reported.

In **Chapter 5b**, we assess if drug concentrations in human saliva could be determined with calibration samples prepared in human serum and perform a recovery test for levofloxacin concentrations in saliva after using sorbent material.

In **Chapter 6a**, we assess the probability of target attainment with currently prescribed Lfx dosages (750–1000 mg once daily) in MDR-TB patients. All three components of PK/PD science, exposure, efficacy and treatment outcomes are incorporated.

In **Chapter 6b**, in a prospective clinical trial, we evaluate the potential role of saliva as an alternative sampling matrix for therapeutic drug monitoring of Lfx in MDR-TB patients.

In **Chapter 7**, we will discuss our findings and elaborate on current and future perspectives for Lfx in TB treatment.

In **Chapter 8**, a summary of the findings of this thesis will be presented.

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