Pharmacological approaches to optimize TB treatment
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Introduction
**An individualized approach**

Tuberculosis (TB) is an ancient infectious disease caused by *Mycobacterium tuberculosis* that has remained a scourge for mankind [1]. TB affects around 10 million people globally each year [2]. Large multicenter clinical trials carried out in the second half of the last century have provided the evidence for current standard therapy with very low failure rates [3]. Of the four first-line drugs, the most important agents are isoniazid and rifampicin [4]. The recommended dose for isoniazid is 5 mg/kg and for rifampicin 10 mg/kg, which means that the dose depends on total body weight [4]; the dosing being based on the dosage used in the aforementioned trials [3]. Only if taken for six months and together with 25 mg/kg pyrazinamide during the first two months of therapy, these drugs have been shown to be highly effective [3].

All of this is only true if the offending *M. tuberculosis* strain is fully susceptible to the first-line agents. Mutations occur randomly with every cell division - resistance to isoniazid depends on the target coded by the *inhA* of *katG* genes, occurring in around $1/10^6$ cell divisions; and in around $1/10^8$ in the *rpoB* gene coding for the target of rifampicin [5]. If *M. tuberculosis* has lost susceptibility to both isoniazid and rifampicin, the strain is called multi-drug resistant (MDR) [2]. Drug-susceptibility testing using critical concentrations of the first-line drugs and molecular tests are used to determine if a *M. tuberculosis* strain is resistant. The critical concentration of a drug is the lowest drug concentration at which 99% of the wild-type *M. tuberculosis* strains cannot grow [6]. Since 1962 the critical concentrations of the first-line anti-TB drugs have been the same [6]. After 1962, new techniques for resistance testing have been developed and increased knowledge on the pharmacokinetics and pharmacodynamics of the anti-TB drugs have been acquired. Therefore, it should be possible to determine more accurate critical concentrations. This hypothesis was confirmed in study by Gumbo et al. in 2010, using a hollow fiber model exposing *M. tuberculosis* strains with drug concentration fluctuations over time, closely resembling what happens in patients with TB [6]. Using this model, and using population pharmacokinetics, the authors used pharmacokinetic/pharmacodynamic targets to determine critical concentrations, which were shown to be much lower than the currently used breakpoints [6]. However, the question remains how we deal and implement these new proposed critical concentrations, knowing that the first-line anti-TB treatment has a success rate of around 85% globally [2]?

Most second-line anti-TB drugs are, just like the first-line anti-TB drugs, dosed based on total body weight [4]. A dosing strategy that is also used, is to divide the
dose in a normal fixed-dose, and a lower dose for patients that have a low total body weight [7]. However, multiple studies show that one-size does not fit all, because more than total body weight alone determines the right dose for treatment of TB [8-13]. Additionally, the prevalence of MDR-TB is increasing, from 17% of all TB cases in 2010 to 27% in 2015 [2]. This also shows that the current treatment strategies might not be sufficient anymore. Therefore, a search for new drugs to treat TB and optimizing the treatment with the currently used anti-TB drugs is warranted.

There is a higher chance of resistance after failure on first-line anti-TB treatment [8]. Additionally, 8% of the MDR-TB patients fail on second-line treatment, and after failed treatment more resistance can be expected with treatment options becoming even more limited [2]. An extreme example is Belarus, where 72% of the previously treated patients develop MDR-TB [2]. Factors that are associated with treatment failure, which is defined as a positive sputum smear or culture after five or more months of treatment, are gender, age, alcohol use, treatment regimen, smoking, co-morbidities such as diabetes mellitus and HIV infection, sputum culture and delayed diagnosis [14-16]. Some of these factors can influence the plasma concentrations of the anti-TB drugs [17]. Low plasma concentrations of anti-TB drugs are associated with treatment failure [10]. Therefore, the adjustment of the dose based on plasma drug concentrations might give us the solution we need to optimize TB treatment and prevent the occurrence of resistance [9].

Adjusting the dose based on drug concentrations in plasma or other matrixes is called therapeutic drug monitoring (TDM). Even though multiple studies have shown that TDM results in positive outcomes, TDM has only recently been included in TB treatment guidelines for the use in selected cases i.e. poor response, drug-drug-interactions, HIV infection and treatment with second-line anti-TB drugs [4,13,18]. This might be due to the costs that are associated with performing TDM [19]. For TDM, one or more blood samples are taken in order to estimate the exposure to the drug and to be able to give an advice on the correct dosage for the individual patient. In order to determine if the dosage adjustment led to a better drug exposure, new samples need to be taken and analysed. This is not only a burden on the patient, but also labour-intensive, time-consuming and expensive. Nevertheless, this is conceivably the best way to individualize and optimize treatment.

There are options to make TDM more patient-friendly, less time-consuming and less expensive. One such option is to reduce the number of sampling time points and venous blood draws by using limited sampling strategies (LSS). With LSS two
to four sampling time points are used to give an estimation of the area under the plasma concentration time cure (AUC) [20]. Another option is dried blood spot (DBS) sampling, a method that uses a finger prick to obtain a blood drop on a special filter paper from which the drug concentration in blood can be determined [21].

Before TDM can be performed for the treatment of TB without restrictions, with or without LSS and DBS, more studies are needed on optimal plasma concentrations of the anti-TB drugs and validation of the techniques for all anti-TB drugs separately. There are target values available for some drugs that are of importance in the treatment of TB, which makes it possible to perform TDM in a small, however important, TB patient population [22]. Nonetheless, target values for many anti-TB drugs are lacking, because the relationship between clinical outcomes and plasma concentrations, as well as the pharmacokinetic properties in different patient groups, are not available for these anti-TB drugs [23].

The aim of this thesis is to explore methods to individualize and optimize drug-susceptible as well as drug-resistant TB treatment.

Outline of the thesis

In chapter 2, we conduct a review on TDM of anti-TB drugs. Firstly, pharmacokinetics and pharmacodynamics of anti-TB drugs are discussed in relation to drug susceptibility, toxicity and efficacy. Next, strategies to perform TDM are explored, as well as molecular resistance testing and host biomarkers that give an idea on the response to treatment. We integrate the results and draft an expert opinion on TDM and the optimization of TB treatment with the support of new techniques such as molecular resistance testing.

In chapter 3 we propose the introduction of a new susceptibility category for TB, dose-dependent intermediate susceptibility. The idea is to treat intermediate susceptible TB with higher doses of the first-line anti-TB drugs in order to prevent failure on first-line drugs, and avoid using second-line anti-TB drugs for patients with these strains. In chapter 3a we discuss the feasibility of this proposal by using computer simulations of higher doses of isoniazid, rifampicin and pyrazinamide. In chapter 3b we study the cost-effectiveness of this approach for a low-income high MDR-TB prevalence setting and a high-income low MDR-TB prevalence setting.
The goal of chapter 4 is to show that TDM does not mean the end of fixed-dose combinations (FDC). For this cause we want to provide a tool for the dose adjustment of FDC based on the outcome of TDM.

DBS sampling can be used for TDM as an alternative for venous sampling. DBS sampling is thought to be a simpler and more patient-friendly method for blood sampling compared to venous sampling. In chapter 5a we study the quality of dried blood spots, to find out if dried blood spots of sufficient quality can be obtained for analysis without any training. The quality of the dried blood spots will be assessed based on four categories with the help of a checklist. In chapter 5b we want to provide a tool to perform TDM with DBS for patients with MDR-TB and HIV co-infection. These patients need many check-ups, which mostly involve blood sampling. The aim of this chapter is to see if these blood collection moments can be optimally combined.

There are limited treatment options for some types of drug-resistant TB, therefore the exploration of other antibiotics is of key importance. In chapter 6a we discuss the carbapenem antibiotics, of which only two are included as an add-on drug in the TB treatment guidelines. In chapter 6b we want to develop a pharmacokinetic model and limited sampling strategy for ertapenem, which is a carbapenem that is not included in the TB treatment guidelines. In chapter 6c we explore the pharmacokinetics of 2000 mg ertapenem and we want to find out if this dose can reach the most important pharmacokinetic/pharmacodynamic target: time above the MIC.

In chapter 8 the general discussion and future perspectives of this thesis can be found. And lastly, in chapter 9 we provide a summary of the findings of this thesis.

References

Introduction


