Pharmacological approaches to optimize TB treatment
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Chapter Su
Summary
The aim of this thesis was to find different ways to individualize and optimize TB treatment with the following objectives: 1) by exploring methods and providing tools to make TDM more feasible, 2) by preventing more toxic and less-effective second-line anti-TB treatment and 3) by exploring other treatment options for the treatment of MDR-TB.

In chapter 2, we studied literature on TDM. The aim of this review was to show what information is still missing and which studies need to be performed before TDM can be added to the TB treatment guidelines. We discussed the pharmacokinetics/pharmacodynamics (PK/PD) in relation to the efficacy and toxicity of the anti-TB drugs, as well drug susceptibility testing and the use of biomarkers to monitor treatment response, which are all helpful tools in the clinical decision making process. Additionally, opportunities were discussed, such as the use of DBS sampling and limited sampling to facilitate or optimize TDM in different settings and whole genome sequencing as part of direct susceptibility testing to find all resistance mutations. Based on the available literature it was concluded that a knowledge gap exist, especially on the proposed integrated approach to optimize TB treatment.

Since 1963 the same critical concentrations of the first-line anti-TB drugs have been used. In 2010, lower critical concentrations were found using a hollow fiber infection model. In chapter 3a, we proposed to use higher doses of the first-line anti-TB drugs isoniazid, rifampicin and pyrazinamide instead of second-line anti-TB drugs to treat the patients that are deemed resistant according to the newly proposed critical concentrations. We chose to call the susceptibility in between the current and proposed critical concentrations, “intermediate susceptibility dose-dependent” (ISDD). We used computer-aided simulations, to model the effect of using a higher dose for strains in the ISDD category. We found that at a isoniazid dose of 900 mg a day, which is three times higher than the regular dose, the ISDD MIC range would be 0.312 – 0.25 mg/L with a critical concentration of 0.5 mg/L. Currently the critical concentration for high-level resistance isoniazid is 1.0 mg/L. For a dose of 1800 mg rifampicin, which also is three times higher than the regular dose, the ISDD MIC range would be 0.0625 – 0.25 mg/L with a critical concentration of 0.5 mg/L. Currently the critical concentration of rifampicin is 1.0 mg/L. Doses of 900 mg isoniazid and 1800 mg rifampicin were shown to be well tolerated in previous studies. Finally, for pyrazinamide we found that a dose of 4 g, which is twice the standard dose, the ISDD MIC range would be 37.5-50 with a critical concentration of 100 mg/L at pH 5.9. The critical concentration currently used is also 100 mg/L.
at pH 5.9. Introducing intermediate susceptibility dose-dependent and treatment with a higher dose of isoniazid, rifampicin and pyrazinamide could be a good alternative for lowering the susceptibility breakpoints.

In chapter 3b we performed a cost-utility analysis to determine the cost-effectiveness of the approach suggested in chapter 3a in the low income, high MDR-TB burden country Belarus and the high income, low MDR-TB burden country the Netherlands. We determined the cost-effectiveness by performing 10,000 Monte Carlo simulations on a Markov model consisting of 14 health states. There was limited information on long-term outcomes of high-dose first-line anti-TB treatment. As a result, assumptions were made on high-dose first-line treatment. By performing sensitivity and scenario analyses we were able to determine which transition probabilities had the largest influence on the outcome of the cost-effectiveness analysis. Using higher doses of the first-line anti-TB drugs isoniazid and rifampicin was shown to be always cost-saving for Belarus. However, varying the assumptions made, sometimes lead to a loss in Quality Adjusted Life Years, which makes the approach not cost-effective in 43% of the cases. For the Netherlands, our approach always was more expensive, but at a willingness-to-pay of 50,000 per Quality Adjusted Life Year, it was cost-effective in 50% of the cases.

Patient non-adherence, which can be caused for instance by a long multi-drug treatment, is one of the reasons for treatment failure. To minimize the number of drugs that need to be ingested every day, fixed-dose combinations (FDCs) consisting of multiple anti-TB drugs, have been implemented in TB treatment programs. Because the idea of TDM is to adjust the dosage of the anti-TB drugs based on the plasma drug concentrations, one might think that this is not compatible with FDCs. In chapter 4 we investigated whether FDCs could be combined with TDM. Based on different TDM results, using the available FDC formulations, a framework was provided, thereby enabling TDM and at the same time still limiting the amount of tablets to be ingested.
As was discussed in chapter 2, DBS sampling can make TDM more feasible because it is thought to be a simpler, less expensive and less invasive method of blood collection. To investigate whether DBS is truly easier compared to venous sampling we conducted an observational study. In chapter 5a we examined the quality of 464 dried blood spots from four different countries, using a checklist consisting of multiple quality indicators. Two independent DBS experts, using the same checklist, evaluated the DBS cards. In total 46 percent of the dried blood spots did not comply with the present quality indicators, which could have an impact the analytical result. The main reasons for rejection were incorrect blood spot collection and insufficient drying.

In chapter 5b we studied the potential opportunities for DBS sampling in patients with MDR-TB and HIV co-infection. Patients with MDR-TB already have a complicated treatment programme, which can become even more complicated if patients are also infected with HIV. Patients have to take 6-10 pills every day and in the first two months of treatment there are two-weekly check-ups for which the patients have to go to hospital. In chapter 5b we show that DBS can be used for viral load quantification and pharmacokinetic assessment in MDR-TB/HIV patients. Serum sodium, potassium, bicarbonate, chloride, blood urea nitrogen, ALAT, ASAT, total bilirubin, serum creatinine, haemoglobin, white cell count and CD4+ count still need to be determined using venous sampling. Nevertheless, steps are being made to quantify the CD4+ count by DBS sampling too, which is preferable because CD4+ count can only be determined in central laboratories in contrast to the remaining quantifications that cannot be performed with DBS, but can be determined in non-central laboratories.

There are limited treatment options for the treatment of MDR-TB and the treatment options become even more cumbersome if there is additional resistance to any of the fluoroquinolones and a second-line injectable, called extensively drug-resistant (XDR)-TB. Consequently, it is of utmost importance to search for alternative treatment options.

In chapter 6a a systematic review was presented on the treatment of drug-resistant TB with carbapenems: biapenem, imipenem, ertapenem, meropenem, faropenem, doripenem and tebipenem. In total 35 studies were included, which were divided in in vitro, in vivo and in human studies. Results of the in vitro studies were highly variable likely due to the chemical instability of the carbapenems in liquid media. Only imipenem, meropenem and ertapenem were studied in human of which most
studies were of retrospective nature. The conclusion of this chapter was that a phase 2 study is needed to determine the position of carbapenems in the treatment of drug-resistant TB.

In chapter 6b we focused on one carbapenem, ertapenem, and developed a pharmacokinetic model with a limited sampling strategy. A two-compartmental model was developed based on 42 healthy volunteers, which was externally validated with the data from 12 MDR-TB patients receiving 1000 mg ertapenem. The exposure, measured as the area-under-the curve for 24 hours (AUC$_{0-24\text{hrs}}$), was shown to be overestimated by a mean percentage of 4.2. Additionally, the most important pharmacokinetic/pharmacodynamic parameter for ertapenem, the free 40 percent of the time above the minimal inhibitory concentration ($f\%T{\geq}\text{MIC}$), was shown to be exceeded by 9 out of 12 MDR-TB patients at a free fraction of 5% and the MIC set at 0.5 mg/L. The limited sampling strategy that performed the best, was sampling at 1 and 5 hours after injection. A time restriction of 0-6 hours was used for clinical applicability.

A previous hollow fiber study showed that 2000 mg ertapenem might be the most effective for the treatment of TB. Therefore, we performed a prospective study to determine the pharmacokinetics of a single intravenous injection of 2000 mg ertapenem in twelve drug-susceptible TB patients in chapter 6c. Blood samples were collected at multiple time points, where after the plasma drug concentrations were modelled. The median AUC to infinity was 2032 h*mg/L, the inter-compartmental clearance was 1.941 L/h and the volume of distribution in the central compartment was 1.514 L. We compared the pharmacokinetics of 2000 mg ertapenem in TB patients with the pharmacokinetics of 1000 mg ertapenem in MDR-TB patients and discovered that the increase in AUC was more than dose-proportional, meaning that the exposure increased more than two times even though the dose was doubled. This was not seen in healthy volunteers. This study also showed that 2000 mg ertapenem in TB patients shows non-linear pharmacokinetic behaviour, probably due to saturation of the major metabolic pathway. Which is something that has not been described for ertapenem before. As we did in chapter 6b, we determined the ability to reach the $f\%T{\geq}\text{MIC}$, which at a MIC of 1.0 mg/L was reached in 11 out of 12 patients.
Summary

In chapter 7 the general discussion and future perspective can be found. In this thesis we have tried to shrink the present knowledge gap for TDM in the treatment of TB. We found that there is limited information on the anti-TB drugs we proposed to do TDM for, but also limited information on the outcomes of TDM to show its added value. We have also discussed the drawbacks of the sampling techniques that could be used to make TDM more feasible. New techniques to optimize TB diagnosis including drug susceptibility or resistance are being developed, as it is one of the focuses of the World Health Organization. Lower susceptibility breakpoints for the first-line anti-TB drugs have already been found. We proposed to use higher doses of the first-line anti-TB drugs instead of second-line anti-TB drugs. However, using higher doses is not widely accepted due to limited information. Another focus of the World Health Organization is the development of new antimicrobials for treatment of TB. We discussed our preference for repurposing antimicrobials for TB treatment instead of or in addition to the development of new antimicrobials. We proposed to perform more studies to be able to find all resistance mutations, to be able to treat all patients with an effective treatment regimen and to determine the added value of TDM and to make it feasible.
Chapter

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