Quantitative pharmacology approaches to inform treatment strategies against tuberculosis

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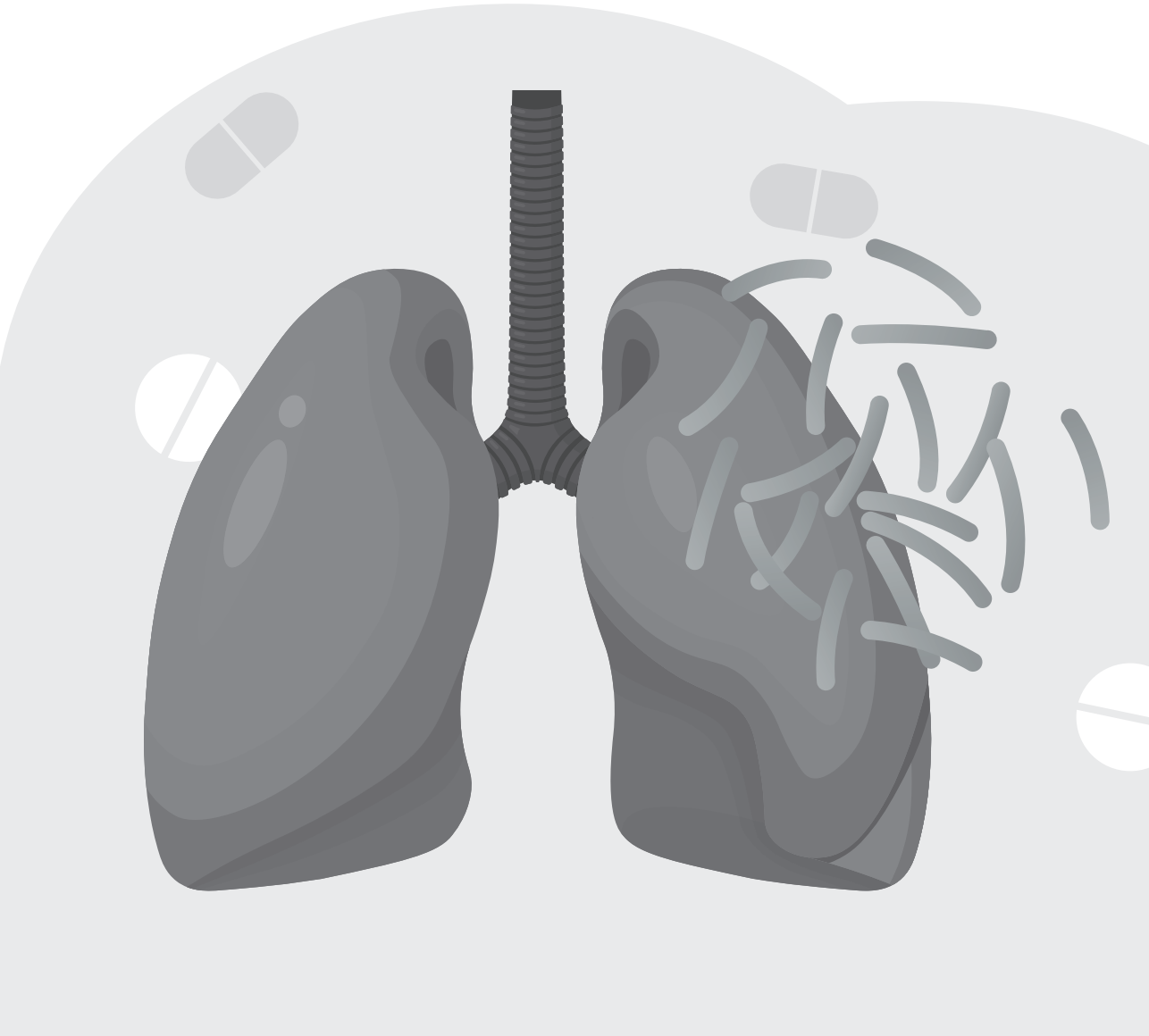
Section V.

Summary and General Discussion



Chapter 9

Summary and General discussion

Tuberculosis (TB) is associated with high morbidity and mortality[1]. Current key challenges against treatment of TB include variability in treatment response, evasion of host immune response, and development of drug resistance. Quantitative pharmacology methods are valuable tools for developing innovative approaches to optimize treatment against Mtb infections to address the challenges effectively and efficiently[2]. In this thesis, we utilized diverse modeling and simulation approaches tailored to specific contexts of use, aiming to tackle the challenges associated with treatment of TB. Key learnings and future perspectives are discussed below divided into themes based on applications of modeling and simulation.

Predictions of drug exposures at sites of action

Understanding the distribution of anti-TB drugs at site-of-action tissues is essential to predict and optimize treatment effects. Lungs and cavitary lung lesion concentrations of bedaquiline and pretomanid have not been collected yet from humans. In **Chapter 4**, translational minimal physiologically-based pharmacokinetic (mPBPK) models of bedaquiline and pretomanid were developed using serum and site-of-action concentrations data from preclinical studies, and serum concentrations data from TB patients. Our model-based simulations suggested that although the currently approved dosing of bedaquiline and pretomanid may achieve lung exposures to exhibit bactericidal activity against replicating bacteria, additional treatment optimization may be required for the eradication of non-replicating bacteria from cavitary lung lesions[3]. In **Chapter 6**, a whole-body PBPK model including central nervous system (CNS) distribution for bedaquiline and its active metabolite, M2, was developed to predict exposures within cerebrospinal fluid (CSF), brain interstitial, and brain intracellular. Bedaquiline and M2 unbound concentrations at target sites, brain interstitial and intracellular, for TB meningitis (TBM) patients, were predicted to be significantly lower than predicted lung intracellular unbound concentrations, suggesting that bedaquiline may not provide an effective treatment option for patients with drug-resistant TBM. In **Chapter 3**, whole-body PBPK models allowed predictions of unbound rifampin and isoniazid exposures at target sites, brain interstitial and intracellular, to evaluate the probability of target attainment for TBM patients. For the drug-susceptible strains, our predictions suggested a high probability (>80%) of target attainment in brain interstitial and intracellular with standard dosing of rifampin and isoniazid, respectively[4]. Consistent with our work, there has been a growing focus on measurement and modeling of lungs and lesion drug concentrations data for anti-TB drugs. For example, mechanistic modeling of seven anti-TB drugs data obtained

from nine different lung lesion types from TB patients demonstrated application of such approach to improve TB treatment outcomes[5,27]. On the other hand, although PBPK models have been applied to predict brain drug concentrations in other therapeutic areas[28], PBPK approach to predict brain drug concentrations of anti-TB drugs have not been published prior to our work.

In the absence of observed relevant target site concentrations data, our models could not be compared against observed data, highlighting a key limitation of such modeling approach. For example, the translational mPBPK models for bedaquiline and pretomanid developed using mice data assumed relatively comparable drug partition coefficients in lungs amongst mice and humans. The CNS PBPK models developed for bedaquiline, rifampin, and isoniazid are reliant on serum and CSF data from patients, and drug distribution to brain interstitial and intracellular compartments is informed by physiological understanding of CNS.

Quantitative pharmacology analyses are reliant on appropriate assumptions and accurate data. In general, the current standard methods for pharmacokinetic (PK) and pharmacodynamic (PD) data collection generally do not include site-of-action measurements; thus, future work could focus more on innovative sampling and measurement methods to obtain relevant and accurate site-of-action PK and PD data[5]. It is not feasible to collect site-of-action samples from large cohorts of patients. Quantitative pharmacology approaches may be used to link data measured using different sampling methods. For example, PK data from a relatively small but significant cohort of patients may be used along with PBPK model-based analyses to quantify the relationships between vascular and site-of-action drug concentrations of anti-TB drugs. Similarly, more refined and precise quantitative relationships could be developed between sputum and site of action Mtb bacterial load data using measurements from a larger pool of patient data than currently available[6,7]. Advancements in newer measurement techniques, for example, imaging techniques capable of measuring PK and PD at the site of action can be very valuable to increasingly support the development of quantitative pharmacology approaches to advance anti-TB therapeutics[8,9].

To summarize, the translational minimal PBPK and whole-body PBPK modeling and simulations performed in this thesis provided insight into target site exposures and target attainment for two first-line, rifampin and isoniazid, and two newer, bedaquiline and pretomanid, anti-TB drugs. These findings can be used to rationally select treatment options for pulmonary TB and TBM patients, as appropriate.

Future advancements in data collection methods combined with quantitative pharmacology approaches are crucial.

Addressing interindividual variability

It is crucial to quantify the interindividual variability affecting PK and PD properties of drugs, as well as the factors influencing this variability. PK of drugs can be affected by various intrinsic factors, e.g., body weight, age, host genotype, and comorbidities, and extrinsic factors, e.g., drug-drug interactions, and smoking status. The PD of drugs is affected by drug exposure at the site-of-action, pathogen genotype, disease severity, etc. Modeling and simulation of anti-TB drugs provide valuable insights into factors affecting interindividual variability to inform treatment optimization approaches[2]. In **Chapter 2**, a top-down population PK modeling approach of ethambutol suggested significant impact of human immunodeficiency virus (HIV) co-infection on reduction in oral bioavailability of ethambutol in pulmonary TB patients. Model-based simulations suggested that a supplementary 400 mg QD ethambutol dosing among HIV/TB co-infected patients may provide a strategy to optimize anti-TB treatment regimens in this high-risk population[10].

In **Chapter 3**, using a bottom-up modeling approach, whole-body PBPK models for rifampin and isoniazid were developed to predict the impact of solute carrier organic anion transporter family member 1B1 (SLCO1B1) genotype on rifampin and N-acetyltransferase 2 (NAT2) genotype on isoniazid, and minimum inhibitory concentrations (MIC) on CNS target attainment following standard and intensified dosing regimen in patients with TBM. The combined effects of genotype and MIC were potent determinants of CNS target attainment of rifampin and isoniazid, providing a direction for future evaluations of precision dosing of rifampin and isoniazid in TBM patients[4]. In **Chapter 4,** translational mPBPK model–based simulations for bedaquiline and pretomanid suggested no significant effects of the size of cavitary lung lesions and body weight on target attainment within lungs and lung lesions in pulmonary TB patients[3]. In **Chapter 5**, the translational mPBPK models of bedaquiline and pretomanid were incorporated within a mechanistic modeling framework to simulate the anti-bacterial efficacy of the combination regimen BPaL. The framework included the dynamics of TB disease progression, drug distribution and available effective fraction into lung and lesions, individual drug effects, PD drug interactions, and the effect of MIC. Our framework predicted no significant impact of covariates, body weight, and MIC, on the overall efficacy of the BPaL combination[11]. In the recent years, mechanistic model-based evaluations

of variability in anti-TB drugs' PK and effects have been performed[27,29-31]. For example, similar to our findings, a published mechanistic model including TB granuloma size predicted no significant impact of granuloma size on duration to granuloma sterilization[31].

The majority of approaches for quantification of covariate effects and interindividual variability have relied on top-down empirical modeling[2]. In this thesis, we also explored how mechanistic model-based approaches can be used to identify covariates that may affect the variability in PK and anti-TB treatment outcome. A key constraint to using mechanistic modeling approach to evaluate interindividual variability is that full mechanistic details of factors that may affect interindividual variability are often not understood a priori. Additionally, models to identify factors affecting interindividual variability are best developed when a large amount of patient level data is available. Moreover, analysis of larger pool of data within mechanistic modeling framework is computationally costly. Future work may consider applications of advanced computational methods, such as Bayesian approaches and machine learning methods using a larger pool of relevant clinical data, along with mechanistic models for robust characterization of covariate–parameter relationships[12,13]. Additionally, various patient data collection methods, including the incorporation of real-world evidence, electronic health records, wearables, etc may be used to support the development of the proposed models. Predictions using such models can be used to rationally guide treatment optimization approaches against TB.

To conclude, the evaluations of the factors affecting PK and PD of anti-TB drugs were demonstrated using top-down and bottom-up modeling approaches depending on available data. These results can be useful to evaluate model-informed precision dosing options. Future efforts should increasingly consider evaluations of data from a variety of sources using mechanistic modeling approaches to guide treatment optimization approaches based on patient factors affecting variability.

Translation from experiments to patients

Accurate translation of PK and PD of new anti-TB drugs from preclinical experiments to patients is essential to rationally design clinical studies. In **Chapter 4**, predictions of exposures in lungs and lesions of TB patients were performed using data from PK studies in mice[3]. This demonstrated the usefulness of the PBPK model-based approach to predict the site of action distribution of anti-TB

drugs, although the predictive power of these models could not be evaluated due to the lack of human lungs and lesion PK data for bedaquiline and pretomanid to date. In **Chapter 5**, translational mPBPK models were extended into a quantitative modeling framework for bedaquiline, pretomanid, and linezolid (BPaL) combination regimen using a variety of in vitro experimental data, such as time-kill experiments in culture, hollow-fiber infection model (HFIM)m, and in vitro PD interaction studies, and PK and early-bactericidal activities data from clinical studies in TB patients. The quantitative framework–based simulations for the combination therapy effects in multidrug resistant TB (MDR-TB) patients matched reasonably well with the observed clinical trial data[11]. In **Chapter 8**, lung bacterial load data from a mice infection study were used to inform metformin-induced autophagy effects within the host-pathogen interactions model. The model-based simulations suggested that adjunctive metformin therapy to first-line anti-TB therapy in TB patients would provide limited effect on reducing the bacterial load. More importantly, the model provided insights into the differences in the overall effects of adjunctive metformin therapy between mice and TB patients (**Chapter 8** Section 8.4)[14]. Similar to our work, application of quantitative framework has also recently been published to efficiently translate effects of anti-TB drugs effects from preclinical to clinical[32,33].

Efficient and accurate preclinical data collection methods are crucial to study the PK and PD of anti-TB drugs and to construct a quantitative framework. Data from preclinical in vivo studies, for example, site of action distribution and immunodynamics data for host-directed therapy (HDTs), sometimes do not directly translate to patients; thus, increasing evaluations of alternative experimental methods combined with modeling and simulations may be beneficial in future. For example, multiple vascularized organ chips may be developed, and data from such a model along with PBPK modeling can be used to predict human serum and target site of action PK of anti-TB drugs efficiently and accurately[15]. Target site PK predictions can then be used along with time-kill experiments at varying drug concentrations from HFIM or in vitro culture experiments to predict early bactericidal activities in patients. Omics experimental data combined with artificial intelligence methods may be evaluated to parameterize QSP models of host-pathogen interactions[16].

In conclusion, we demonstrated the importance of quantitative approaches to compile the findings from various preclinical data into a decision-making framework. It is important to continue to develop innovative data collection methods and to use model-informed approaches to overcome preclinical to patient translational challenges.

Treatment of multi-drug resistant tuberculosis

MDR-TB is caused by Mtb strains resistant against both rifampin and isoniazid, two key first-line anti-TB drugs. The recent approval of the new combination regimen BPaL against MDR-TB has been a key step towards the resolution of the global health challenge of drug-resistant tuberculosis. Some safety and adherence concerns remain with the BPaL-approved dosing schedules[17,18]. In **Chapter 5**, a quantitative modeling framework was developed for the BPaL combination regimen. The framework adequately described the observed antibacterial activity data in patients following monotherapy for each drug and approved BPaL dosing. The simulations for approved and alternative dosing regimens suggested that similar efficacy could be attained by using alternative dosages of bedaquiline and linezolid in the BPaL combination. The alternative dosage has the potential to enhance safety and adherence. Additionally, the simulations provided insights into the approximate treatment duration required for the eradication of both replicating and non-replicating Mtb from lung lesions. The BPaL quantitative platform can be used to assess treatment optimization approaches, including dosing regimen and duration of treatment predictions to eradicate both replicating- and non-replicating bacteria from lungs and lesions to ensure appropriate treatment and to avoid relapse of MDR-TB patients.[11] In alignment with our predictions, recently published clinical data and top-down model-based analysis of the data evaluating the approved and alternative linezolid dosing predicted no significant difference in efficacy between the approved and alternative linezolid doses in MDR-TB patients[18,29].

To eradicate TB in the future, treatment approaches should consider not only treatment of drug-resistant TB but also prevention of resistance development. To accomplish this goal, exploration of rigorous treatment approaches could be employed. As discussed, quantitative platforms could be used to guide the optimization of dosing regimens and treatment duration based on patient factors. For example, individual drugs' MIC, could be used to guide dosing and treatment duration to ensure eradication of both replicating- and non-replicating Mtb. Models can be used to ensure optimal exposures at the target site of action to ensure adequate efficacy, to prevent the development of drug resistance, and to manage safety concerns[19,20]. This may help increase patient adherence and avoid treatment interruptions that play a crucial role in achieving overall positive treatment outcomes in MDR-TB patients. Additionally, future work could consider extension of our BPaL quantitative framework to include PK and PD of additional drugs to guide the selection of optimal combination regimens based on patient factors[21].

To summarize, we presented a quantitative framework for predicting dosing regimens of BPaL combination treatment in MDR-TB patients. The framework can be used to evaluate treatment optimization approaches for the BPaL combination. We propose future development and use of quantitative frameworks to support the development of new treatment approaches against MDR-TB.

Treatment of tuberculosis meningitis

Relatively rare but the most severe form of TB, TBM, is associated with high morbidity and mortality rates to date. In this thesis, model-based approaches to predict PK exposures within CNS to evaluate intensified dosing schedules were explored (Section 91.1). As discussed in **Chapter 3**, intensified dosing schedules of rifampin and isoniazid are required for a subset of patients based on pharmacogenetics and Mtb MIC to achieve therapeutically desirable exposures within the brain for the treatment of TBM. Additionally, the cases of rifampin- and isoniazid-resistant TBM are on the rise and there is no standard-of-care treatment regimen that is safe and efficacious for those patients. Therefore, newer anti-TB drugs, such as bedaquiline, are being evaluated as a treatment option for such cases[9,22]. In **Chapter 6**, we predicted bedaquiline unbound concentrations within brain intracellular compartments to be significantly lower than predicted lung intracellular concentrations range using a whole-body PBPK modeling approach. This suggested that bedaquiline may not be suitable for the treatment of drug-resistant TBM and that additional newer anti-TB drugs should be evaluated for this population.

In this thesis, we introduced PBPK approach to predict brain drug concentrations of anti-TB drugs for the treatment of TBM. A limitation of this approach is that it is not feasible to collect samples from patients to be able to compare model predictions against. However, as we showcased, observed CSF drug concentrations combined with PBPK approach and in vitro MIC data may provide a broader view of overall effects of anti-TB drugs for treatment of TBM.

The current first-line treatment regimen against TBM is ineffective in a high number of patients and intensified rifampin and/or isoniazid dosing is often required[23,24]. Future work may focus on the implementation of a PBPK-based modeling framework to guide dose and dosing regimen optimization, including intensified dosing as needed, to ensure optimal CNS exposure based on patient factors, such as patient genotype, individual MIC, body weight, etc. Although intensified

rifampin and isoniazid dosing provide improved efficacy in TBM patients compared to standard dosing, they can be associated with increased safety concerns. There seems to be an apparent need to further evaluate current newer anti-TB drugs for TBM patients, and increasing the use of quantitative pharmacology methods could offer an efficient and reliable strategy. In silico approaches can also help identify desired physicochemical and kinetic properties to guide the discovery of new anti-TB drugs with high CNS penetration and anti-TB efficacy.

To conclude, the use of PBPK models to predict brain target attainment for rifampin and isoniazid to identify TBM patient populations who may require intensified treatment approaches. Additionally, the use of the PBPK approach to predict the suitability of newer drugs, such as bedaquiline, for the treatment of TBM was demonstrated. Further efforts in the discovery and development of treatment approaches for the effective treatment of TBM, especially drug-resistant TBM, are essential.

Host-directed therapies to harness the power of immune response to fight against tuberculosis

HDTs that modulate host-pathogen interactions to enhance the effect of host immune response against Mtb offer innovative treatment options and are being evaluated. In **Chapter 7**, key HDT mechanisms were reviewed, such as autophagy induction, regulation of host epigenetics, and modulation of cytokine and T-cell responses. Next, the use of QSP modeling approaches was proposed to facilitate the design of novel HDT combination treatment strategies and discussed the components of QSP models[14]. In **Chapter 8**, we exhibited an example of using QSP modeling with experimental data to predict the effects of metformin-associated autophagy induction combined with first-line anti-TB treatment in patients. The model-based simulations for adjunctive metformin therapy in newly diagnosed patients suggested a limited yet dose-dependent effect of metformin on reducing the intracellular bacterial load when overall bacterial load is low, and late during antibiotic treatment[14]. This framework may be extended to guide the design of HDTs against Mtb. Literature-based examples of evaluations of host-pathogen interactions mathematical models to evaluate vaccine candidates are available; however, such models have not been utilized to support evaluations of HDTs prior to our work[34].

Future work could consider an extension of the QSP framework (**Chapter 8**) with additional HDT pathways as illustrated in **Chapter 7**. Simulations using such models can be used to identify HDT targets to evaluate and design treatment approaches. Moreover, integrating the HDT QSP model with the extended multistate tuberculosis pharmacometrics model - PKPD quantitative framework (**Chapter 5**) may be valuable in designing optimal HDT and anti-TB antibiotic combinations to fight against MDR-TB and to prevent the development of resistance against anti-TB drugs[25,26]. As the development of QSP models for HDTs in the context of drug-host-pathogen interactions is contingent upon comprehensive mechanistic understanding, future work could focus on addressing the current knowledge gaps through efforts to collect relevant experimental data and using QSP in learn-and-confirm paradigm[35].

In conclusion, the content and applications of QSP models to efficiently evaluate HDT treatment approaches against Mtb were discussed. Then, an example of the proposed QSP model-based approach was demonstrated using metformin as an autophagy induced combined with first-line anti-TB treatment.

Conclusions

In this thesis, we demonstrated that it is imperative to increasingly employ model-informed drug development and treatment optimization methodologies to effectively combat TB. We applied modeling and simulation approaches to tackle key TB treatment challenges, including target site exposures, factors affecting interindividual variability, translation of experimental findings to patients, and enhancing treatment of drug resistance TB and TBM. Several takeaways were derived from this work. For instance, PBPK model-based predictions of target site exposures after accounting for intrinsic and extrinsic factors affecting interindividual variability in PK can be useful to optimize dosing schedules anti-TB drugs to attain optimal Mtb killing. PBPK models are also well suited to understand tissue distribution and binding characteristics of drugs enabling translational prediction of a drug's viability for treating different forms of TB, including, pulmonary TB and TBM. Similarly, quantitative frameworks, e.g., BPaL combination framework, can be useful to develop new combination regimens and to evaluate treatment optimization approaches for combination regimens against TB, especially drug-resistant TB. Moreover, we discussed leveraging host-pathogen interactions for treatment of TB and showcased the use of QSP for evaluating adjunctive HDTs for TB treatment. A key limitation to applying quantitative

pharmacology approaches to inform anti-TB treatment approaches is often the availability of relevant mechanistic information and data. Future efforts should consider collecting and incorporating data from diverse sources into mechanistic modeling frameworks to guide treatment approaches against TB more effectively and efficiently.

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