Pharmacometrics in tuberculosis: progress and opportunities

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Abstract

Tuberculosis (TB) remains one of the leading causes of death by a communicable agent, infecting up to one-quarter of the world’s population, predominantly in disadvantaged communities. Pharmacometrics employ quantitative mathematical models to describe the relationships between pharmacokinetics and pharmacodynamics, and to predict drug doses, exposures and responses. Pharmacometric approaches have provided a scientific basis for improved dosing of anti-TB drugs and concomitantly administered antiretrovirals at the population level. The development of modelling frameworks including physiologically based pharmacokinetics, quantitative systems pharmacology and machine learning provides an opportunity to extend the role of pharmacometrics to in-silico quantification of drug–drug interactions, prediction of doses for special populations, dose optimization and individualization, and understanding the complex exposure–response relationships of multi-drug regimens in terms of both efficacy and safety, informing regimen design for future study. This short, clinically focused review explores what has been done, and what opportunities exist for pharmacometrics to impact TB pharmacotherapy.

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1. Introduction

Tuberculosis (TB) is one of the leading causes of death by a communicable agent. Mycobacterium tuberculosis infects approximately one-quarter of the global population, predominantly in low- and middle-income countries [1]. Approximately 10 million people develop TB and 1.4 million [15% living with human immunodeficiency virus (HIV)] die each year, despite TB being preventable and curable.

Current treatment regimens for drug-susceptible TB are effective, but the 6-month standard-of-care multi-drug regimen (including rifampicin, isoniazid and pyrazinamide, with or without ethambutol) is onerous, despite recent work towards shorter regimens [2,3] and dose optimization [4–6]. To simplify treatment and facilitate drug supply and distribution, TB control programmes employ standardized regimens delivered as fixed-dose combination (FDC) tablets [7]. Multi-drug-resistant TB (MDR-TB) is treated with longer regimens, including second-line drugs, and has a considerably lower success rate, although the advent of new drugs such as bedaquiline [8], delamanid [9] and pretomanid [10] has been transformative. However, there remains a significant unmet need for new therapeutics, better-optimized doses and drug combinations, and routes of administration, for which novel and innovative techniques are needed [11].

Pharmacometrics encompass the development and application of interdisciplinary quantitative models to understand the relationships between dose, exposure, efficacy and safety. Using pharmacokinetic (PK) and pharmacodynamic (PD) data, it applies a wide range of mechanistic and empirical techniques to describe and predict complex biological systems [12], and is applied throughout drug development to improve decision-making, accelerate development and reduce costs. Pharmacometrics form the basis for model-informed precision dosing (MiPD), which provides optimized individual dosing based on individual drug concentrations, demographics and population PK models [13].

Artificial intelligence (AI) and machine learning (ML) techniques are becoming more frequently applied to healthcare [14], and their use in pharmacometrics is no exception [15]. Within the pharma-
ceutical industry, they have been applied successfully to drug discovery, and there is an opportunity to utilize classical pharmacometric tools together with AI/ML in order to enhance drug development [16]. Pharmacometrics continue to make important contributions to the management of TB [17]. The authors believe that pharmacometrics have the potential to accelerate TB drug development and to further optimize treatment, particularly with respect to dose–exposure–response and treatment individualization [18,19]. This review investigated the impact of pharmacometrics on the treatment of TB, and future opportunities for the application of quantitative modelling in this area. The authors focused primarily on clinical aspects, although the review touches briefly on preclinical aspects where relevant.

2. Dose–exposure relationships in patients

Population PK analyses (employing non-linear mixed effects methods) describe empirical compartmental models of drug disposition. The effect of body size is often accounted for using allometric scaling (by weight or fat-free mass, for example) on volume and clearance [20], and maturation functions are commonly applied in young children [21]. Relationships between model parameters and covariates such as sex, race, nutrition, disease and genetic variants can be included in population PK models to explain observed differences in exposure between individuals, usually in blood or plasma, although concentrations can be modelled in other compartments as well if suitable samples are available [22]. Rifampicin concentration–time profiles in multiple compartments and organs collected using radiolabelled drug and positron emission tomography with computed tomography (PET-CT) have been modelled and used to predict intraloesal rifampicin concentrations [23]. This modelling was integrated with hollow-fibre bacterrial kill curve experiments to provide estimates on the rifampicin dosing required to achieve cure in 4 months. The population PK of first-line TB drugs have been described extensively in adults and children with TB using pharmacometric models, and models have been published for most medicines used in the treatment of MDR-TB. Although a detailed overview is beyond the scope of this review, comprehensive summaries have been provided by others [24,25]. Population PK models have five important roles: providing a basis for exposure–response analysis and optimization of doses; facilitating evaluation of PK in special populations in which limited data may be available; optimizing paediatric treatment; enabling individualized dosing using Bayesian predictions; and supporting efficient evaluation of drug–drug interactions (DDIs) in combination therapies.

Dosing of anti-TB drugs has, until recently, been based on uniform milligram per kilogram (mg/kg) doses across weight bands. Population models have demonstrated that this approach leads to reduced exposures in smaller individuals and children, and provides an opportunity to optimize dosing. Recent population PK analyses of first-line drugs and rifapentine have demonstrated that simplified weight bands, or even flat dosing, reduces variability in drug exposures [26] between individuals compared with the weight-based approach [27–29]. Population PK models have found that reduced absorption exacerbates low exposures to rifampicin and isoniazid in young children [30–32]. Underexposure to first-line drugs is common in children, although immature clearance tends to mitigate these effects in young infants. A pharmacometric approach to optimize both content and weight-based individualization strategies for first-line drugs in FDCs has been developed [33,34]. Work has been undertaken on optimizing paediatric dosing of second-line drugs [35–38], although evidence to support paediatric dosing of newer second-line agents remains to be established. Less is known about second-line treatment options in pregnancy, but several initiatives utilizing opportunistic PK sampling in women treated for MDR-TB are ongoing, and pharmacometric approaches will be applied to interpret the results.

Population models are well suited to optimizing doses for special populations and have been used to characterize the impact of HIV co-infection, malnutrition and pregnancy on first-line drugs. While many studies have applied standard non-compartmental analysis (NCA) approaches, population models are a better tool for separating correlated factors such as HIV infection and ARV treatment, and for determining the primary parameters (such as bioavailability or clearance) of highest relevance. Population PK can be used with sparse data, uneven sampling designs and missing data, and can be used for simulation of new regimens and new populations.

The individualization of drug doses using limited PK sampling has been advocated in TB treatment [39]; population PK models provide a useful platform for MIPD. Given the dose, the time of the dose, and the individual’s demographic characteristics, models can be used to estimate secondary PK parameters (e.g. area under the concentration–time curve and peak concentration) from a minimum of samples, and to predict individual optimal dosing relative to a given target [13,40,41]. MIPD has distinct advantages relative to therapeutic drug monitoring (TDM), which, although widely used, can only provide information on whether exposures are within a desired range. MIPD, by contrast, can provide the clinician with tools to calculate the dose meeting a predefined target concentration more accurately, by taking into account factors affecting dose–exposure–response relationships, such as the patient’s body size, sex, ethnicity and age, as identified by PK/PD modelling. This approach has the potential to be more accurate and therefore effective, than currently used weight-based dosing bands.

DDIs are common in TB due to the complex cocktails of drugs that patients – particularly those living with HIV – must take daily. Preclinical data can be used to predict DDIs, and in turn the total efficacy of a combination in relation to monotherapy and expected additivity (the sum of all drug effects when given alone). Rifampicin and rifapentine are the most prominent sources of DDIs in TB treatment, substantially reducing exposure to many concomitant drugs through potent induction of several P450 enzymes and drug transporters [42], a particular problem with antiretrovirals (ARVs), such as protease and integrase inhibitors. Population models have been used to describe complex DDIs in patients with TB/HIV [43,44], have identified interactions within anti-TB regimens [45–48], and have been used to predict adjusted dosing approaches [49]. It is difficult to characterize DDIs for compounds with long half-lives accurately through NCA in standard phase I type studies, and model-based analysis provides an effective alternative [50]. The semi-mechanistic basis of population PK models describes the specific impact of DDIs on absorption, distribution, metabolism or excretion, and can account for the route of administration. Interactions affecting hepatic enzymes, for example, impact exposure for both orally and intravenously administered drugs, whereas induction of gut transporters or enzymes only affects orally administered drugs. Both scenarios can be readily modelled.

Physiologically based PK (PBPK) models provide a bottom-up mechanistic approach, useful for initial dose prediction but also providing an efficient pathway for assessing DDIs in adults and children, while reducing the need to expose human participants to experimental approaches [51]. The effect of genetic polymorphisms of N-acetyl transferase 2 on drug interactions with isoniazid has been studied using this approach [52], and there are obvious benefits to applying the same method to evaluating rifampicin DDIs. The development of tools to integrate such systems approaches with data-driven population pharmacometric modelling built on clinical
data would extend the scope of applications and improve confidence in the predictions [53].

Although still a relatively undeveloped area, experience with the application of ML/AI approaches for investigating dose–exposure relationships is growing – an application of ML to predict rifampicin PK is a recent example [16].

3. Clinical drug exposure–response relationships

Doses of rifampicin two- to five-fold higher than those in established use are being evaluated for their treatment-shortening potential, highlighting the need to understand PK/PD relationships in patients with TB in order to optimize treatment. Empirical methods have been applied to clinical cohorts to define exposure–response relationships for efficacy and toxicity [54,55], and pharmacometric and ML approaches have been used in patients on multi-drug therapy to identify the drugs and exposure metrics most critically driving treatment response [3,54–60]. Patterns of early bacillary clearance characterized by longitudinal quantitative modelling have been linked to risk of recurrence [60]. Model-based analysis of repeated sputum cultures, using colony-forming units or time-to positivity in liquid cultures, improves power to detect exposure–response relationships [61,62] in comparison with culture conversion, which is typically analysed as a proportion or as a time-to-event variable.

Pharmacometric analysis of trial data has proven to have a higher power to detect significant exposure–response relationships, as seen in the PanACEA HIGHRI1 trial [4]. Although not identified by conventional statistical analysis, a significant exposure–response relationship between rifampicin exposure and time-to-positivity in mycobacterial growth incubator tubes was detected using model-based analysis [63].

Models may integrate biomarker information with other data, such as the recently developed rRNA synthesis ratio, which measures the proportions of phenotypically different M. tuberculosis [64]; data from imaging methods such as PET-CT to characterize the evolution of lesions; and genomic, transcriptomic and proteomic signatures of both pathogen and host [65]. Model-based risk stratification studies suggest that treatment design should also account for individual patient characteristics, including the extent of lung cavitation, mycobacterial load in baseline sputum, sex, HIV infection, treatment adherence and early treatment response [18].

A lack of accurate markers of treatment response, inexact extrapolation of PK over time, multi-collinearity and complex interactions in high-dimensional data with multiple time-varying covariates, and heterogeneity within and between study populations remain important challenges [66]. Pooled exposure–response models linking biomarkers of treatment response across different studies may improve understanding of within- and between-study differences, improving precision and confidence in associated findings.

Defining dose-related toxicity of one or more drugs in multi-drug regimens is a challenge recently taken up using pharmacometric approaches, adjusting for baseline measures of toxicity markers, other risk factors, and shared toxicity with companion drugs. Examples include newly presented exposure–response analyses of QT interval prolongation, which can be caused by multiple anti-TB drugs including bedaquiline, delamanid, clofazimine and moxifloxacin [67–69]. In ongoing efforts to define the optimal dose of rifampicin, a proportional odds model for ordered categorical data has been used to describe the probability of tolerability-related adverse events during the first week of treatment [70], and a similar approach was also utilized to characterize neuropathy in linezolid treatment [71]. The same authors developed longitudinal toxicodynamic models describing haemoglobin level and platelet count during linezolid treatment. Combining exposure–response models for efficacy and safety provides a powerful strategy to inform optimized and personalized dosing.

4. Modelling platforms and quantitative systems pharmacology

Multiple levels of data can be incorporated using more complex quantitative systems pharmacology (QSP) models. Translation of data from in-vitro and in-vivo experiments to patients requires integration of data from a range of platforms.

The QSP approach combines different levels of data. It can be applied to scaling preclinical data to humans, translating plasma drug exposures into dynamic concentrations at sites of infection, characterizing penetration of free drug into infected cells and drug distribution in diseased lesions, and describing the flux of drug across the mycobacterial cell wall and membrane to cellular targets. It can be employed to account for immunity, and integrate the effects of multiple drugs [72]. The exploration of phenotypic differences in persistent TB bacteria between in-vitro systems and patient sputum [73]; computational models of granuloma formation and function [74]; models describing the spatio-temporal distribution of drugs in granulomas and cavitary TB lesions [75], the multi-state TB pharmacometric (MTP) model, which provides predictions of the change in bacterial counts for fast-, slow- and non-multiplying bacterial sub-populations, with and without drug effects [76,77]; and models linking the MTP with the General Pharmacodynamic Interaction (GPDI) model to account for the PD interactions between concomitantly administered drugs [78–80], are examples of recently developed ‘sub-systems’ platforms contributing to ever-more complex models informing optimal drug combinations and doses [81–86]. Models describing drug distribution to cerebrospinal fluid (CSF) have proven useful in informing the treatment of TB meningitis, with recent work linking low rifampicin [87] and isoniazid [88] concentrations in CSF to negative outcomes. The MTP-GPDI model using QSP model elements has been shown to successfully predict early clinical trial data using preclinical information together with translational factors [79,80].

Pharmacometric analyses have an important role in translational medicine and vertical integration of findings from drug discovery to confirmatory trials. A great deal of important work is currently ongoing in the preclinical space [89–92], most notably with the hollow-fibre infection model [23,93,94] and rabbit [23,95] and murine [96] infection models, although a detailed discussion of this aspect of the field is beyond the scope of this review. In the exposure–response analysis of rifapentine in two phase II clinical trials [58], large cavities were shown to be a predictor of unfavourable outcome; this finding was corroborated in a recent phase III confirmatory trial – the TBTC Study 31/A5349 [2] – and explained by non-clinical studies in a rabbit model of active TB which found that rifapentine penetrates lesions poorly compared with rifampin [97].

Lesion penetration into cavities is an increasingly important drug attribute; non-clinical animal models combined with modelling approaches allow for quantitative clinical predictions of intralesion concentrations. These studies can give a mechanistic rationale for the contribution of an individual drug to a multi-drug regimen, and have explained the efficacy of moxifloxacin [98,99], rifampicin [97], ethambutol [100], kanamycin and amikacin [101]. Using models to bridge non-clinical data with clinical outcome enables insights that are otherwise too costly or unethical.

Beyond physiological site-of-action PK, mechanistic modelling can translate efficacy results from non-clinical models to clinical outcomes. The largest database of efficacy data for single drug and combination regimens has been generated using the Balb/c mouse model. Using common principles of pharmacometrics, the database can be leveraged to develop an in-vivo PK/PD model, and in combination with population PK models, clinical outcomes can be simu-
lated. This technique was applied to simulate the outcomes of two phase III trials [102].

5. Opportunities and outlook

This review provides a high-level overview of the ways in which pharmacometrics continue to contribute to TB pharmacotherapy. Population PK models have been extended to understanding dose–exposure relationships for many anti-TB drugs. Initiatives and ideas from pharmacometricians are central in the ongoing process to improve the design of, and data collection in, TB clinical trials [103]. Opportunities remain with respect to optimization of dosing regimens in different contexts, most notably in paediatrics and DDI, and ML/AI approaches have the potential to be transformative.

Innovations such as the MTP model with CPDI are examples of modelling platforms which will boost efficiency and democratize access to advanced quantitative tools without the need for local pharmacometric expertise; the development of common tools and standards for data collection will improve this further. Pharmacometric models are well suited to online deployment as interactive tools for exploring dose–exposure–response relationships in different populations and settings.

As technology and understanding evolves, and as more complex models and approaches become possible, the power of pharmacometrics to inform TB treatment will become ever more decisive. Strides have been made in linking dose and exposure to clinical outcomes, but there is more to do, especially with regards to inclusion of novel biomarkers. Increasingly complex models enriching inherently limited data obtained from clinical studies through integration with pharmacometric and QSP models will accelerate regimen design.

The use of pharmacometrics to improve TB treatment is not without its challenges, of course. The results of research are often complex, requiring interpretation, and clear communication of how the results might be translated into improved care. The vast majority of TB cases globally are treated using standard regimens, and no TDM or MIPD is performed. Pharmacometrics have had a significant impact on informing high-level decision making, specifically with respect to changes to recommended dosing regimens, but TDM and MIPD can only be applied effectively where sufficient infrastructure and resources are available.

Although model-based approaches have made great contributions to the field already, the authors believe that more is not only possible, but essential. There remain many untapped opportunities to use mathematical modelling and simulation to reduce the burden of TB around the globe.

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Competing interests

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