The implications of model-informed drug discovery and development for tuberculosis

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ABSTRACT

Despite promising advances in the field and highly effective first-line treatment, an estimated 9.6 million people are still infected with tuberculosis. Innovative methods are required to effectively transition the growing number of compounds into novel combination regimens. However, progression of compounds into patients occurs despite the lack of clear understanding of the pharmacokinetic-pharmacodynamic relationships. The PreDiCT-TB consortium was established in response to the existing gaps in tuberculosis drug development. The aim of the consortium is to develop new preclinical tools in concert with an *in silico* model-based approach, grounded in pharmacokinetic-pharmacodynamic principles. This paper highlights the potential impact of such an integrated framework on various stages in tuberculosis drug development and on the dose rationale for drug combinations.

Introduction

The development of new combination therapies for tuberculosis (TB) is lengthy and costly **(1)**. Despite promising advances in the field, innovative methods are still needed to effectively transition the growing number of compounds into novel combination regimens. Among other things it is essential to shorten current treatment and tackle multidrug resistant tuberculosis.

Shift in paradigm in tuberculosis drug development: reality or fiction?

The disappointing results from all recent Phase 3 trials **(2-5)** clearly demonstrate that a shift in paradigm is needed in TB drug development. Insufficient efficacy is the main cause for failures in clinical drug development **(6, 7)**. Achieving efficacious drug exposure at the site of action is imperative for producing the desired response, i.e., reducing or preventing relapses. Nevertheless, the decision making process in Phase 2 or 3 trials has remained empirical and recent development programs have progressed with limited pharmacokinetic-pharmacodynamic (PKPD) knowledge to support the dose selection and study design. Clearly, dose selection must be based on evaluation of the pharmacokinetic properties and concentration-effect (PKPD) relationship of each drug, rather than by trial and error. Such concerns are also applicable to the most common approach, i.e., the use of currently approved doses for the background standard of care treatment.

The challenges above are compounded by another major bottleneck in the development pathway in that current regulatory guidelines support the need for a long and often poorly informative range of studies. The rationale for testing different doses, regimens and sequence of add-on drug of each potential combination is clearly inefficient **(8)**. At least six years (an

estimated one year for Phase 1, two years for Phase 2, and three years for Phase 3) are required to develop one new antibiotic **(1)**, whereas more than two decades (4x6 years) would be needed for the development and approval of a completely novel regimen consisting of four new antibiotics through successive trials **(1)**. This paper focuses on how an integrated PKPD/disease modelling and simulation framework, also known as model-informed drug discovery and development (MID3), could accelerate the development of novel combination therapies and highlight the potential impact of such framework to inform more robust decision making in TB drug development.

Historically, the approval of current first short-course therapy for TB was preceded by sequential testing of promising candidates in preclinical experiments, which were then followed by clinical studies under the sponsorship of the British Medical Research Council (BMRC) in the 1970s and 1980s **(9)**. These drugs were approved based on the traditional paradigm in drug development in which the progression of candidates depended on a sequential decision-making process. i.e., each phase is considered as discrete steps that are successfully completed as soon as pre-defined targets or criteria are met. This approach, however, does not provide the flexibility that is required to rapidly and effectively assess multiple new combination regimens in a single development programme. Yet, new anti-TB drugs or combinations are still assessed according to the same linear pathway before moving to large trials in which the new drug is added to or used as substitution to one of the drugs in the standard regimen **(10, 11)**. Most alarmingly is the lack of a strong scientific basis for the selection of doses and dosing regimens for one of the major poverty-related diseases.

PreDiCT-TB: a quantitative framework for tuberculosis drug development

A robust quantitative framework is required to integrate data and facilitate effective translation of preclinical findings to humans. To that purpose PreDiCT-TB, an Innovative Medicines Initiative (IMI)-funded project consisting of pharmaceutical R&D and academic partners, has proposed the development of model-informed approaches to address some of the existing gaps in TB drug development. In particular, attention is given to opportunities for improved evidence generation as well as evidence synthesis for the evaluation of new, more effective combinations of treatments. PKPD/disease modelling and simulation have been established as powerful tools for the characterisation of efficacy and safety in other therapeutic areas **(12, 13)**. Its impact on therapeutics and drug development has been reviewed extensively **(14)**. A formal modelling framework that integrates data arising from novel or existing preclinical models and historical clinical studies is envisaged to inform decision-making at different stages of development, i.e., optimisation of experimental protocols, sampling schemes and design the subsequent studies or termination of the project (**15**). Most importantly it enables comprehensive evaluation of the dose rationale (**16**).

Within PreDiCT-TB, a set of carefully selected anti-TB drugs (licensed and unlicensed) are being evaluated in standard and novel preclinical models. In parallel, a comprehensive database consisting of individual patient data from historical clinical trials will be established for use as a reference for evaluating the performance of multiple anti-TB drug regimens, as assessed by preclinical models. These results will be used to refine experimental protocol conditions and identify experimental designs that are most informative, i.e., provide evidence of the underlying concentration-effect relationships or support the translation of drug effects in humans (**17**). Both preclinical and clinical data will then contribute to the development and validation of a PKPD/disease modelling and simulation framework, which is intended to support the progression of candidate molecules into clinical development. Among the key

deliverables of the consortium are the evaluation of (adaptive) study designs and translational research platforms for novel combination therapies for TB (**Figure 1 and 2**). An overview of current recommendations for implementation of a model-informed approach as envisaged by PreDiCT-TB is presented in **Error! Reference source not found.**.

Evidence generation and evidence synthesis at candidate selection

The availability of preclinical models that reflect key human pathological features of tuberculosis infection would be a valuable tool for translating pharmacokinetic-pharmacodynamic (PKPD) concepts, offering a strong rationale for clinical trial designs **(19, 20)**. If designed properly, such experiments could also facilitate the characterisation of PKPD relationships of drugs in combination therapies, providing insight into exposure levels that correspond with optimal effect. Based on this approach, pre-clinical findings should form the basis for dose selection in humans and support the design of subsequent clinical studies **(19)**.

TB has seen many exciting advances in preclinical research **(21, 22)**. *In vitro* and animal models are becoming more sophisticated and have enabled us to generate more insight regarding the immunopathology of the disease and the interaction between various *Mycobacterium tuberculosi*s (Mtb) subpopulations **(23)**. However, given major differences in TB susceptibility and histopathology that currently exist between animal model, it is unlikely that a single experimental system will become available that could fully mimic the infection process in humans. In addition, large variability is observed in *in vivo* efficacy studies depending on the choice of Mtb strain **(24).** In most cases, these experiments rely on limited information about drug combinations, range of doses or dosing intervals. Consequently, translation of preclinical

data to inform suitable combinations and appropriate dosing regimens in clinical trials is anything but accurate.

PKPD/disease models can be developed to systematically characterise the differences in disease condition and evaluate the impact of combination therapies on the PKPD relationship of backbone treatment in various animal models. It can be anticipated that the use of such models may allow 1) the refinement of experimental protocols, consequently reducing the sample size needed in preclinical studies without compromising the precision of information derived from the experiment, 2) inform prioritization of the best drug combinations to be tested in clinical development, and 3) systematically evaluate the performance of various preclinical models against available human data. It should be emphasised that even if shortcomings were to be found in the translation of findings, the use of a model-informed approach does represent a considerable improvement in terms of the 3 Rs (reduction, replacement and refinement).

Evidence generation and evidence synthesis during clinical drug development

Once the best predictive preclinical models are identified, clinical trial simulations (CTS) can be harnessed to evaluate an unlimited number of experimental scenarios (i.e. drug combinations, dose selection, sampling times, and sample sizes) on a systematic manner to identify the best clinical study design. For example, CTS has been successfully used to support selection of the dose range of antibiotics in phase II/III studies by integrating data on the distribution of MICs for clinical isolates with the PD target(s) developed from animal models of infection and pharmacokinetic characteristics of the compound **(25)**. By contrast, Phase 2 studies have often ignored pharmacokinetic variability and other sources of variation in

treatment response in the target patient population, which need to be accounted for when exploring the dose–exposure-response relationship. The impact of CTS during clinical development by means of providing stronger support for regulatory approval and labelling has been established in other therapeutic area **(12, 26)** and acknowledged by the regulatory agencies **(27)**. Given that only a limited number of combinations can be tested in humans, it is crucial to harness methods that facilitate more robust study design and dose range selection prior to the start of the actual trial. If necessary, data from Phase 2a can be used prospectively to refine the PKPD/disease model and increase its performance to assess the best Phase 2b and 3 study protocol (i.e. patient population, dose, sample size, sampling time, treatment duration and drug combinations). Moreover, additional factors such as different compliance patterns and other co-morbidities can be included into the simulation scenarios when evaluating the dose rationale for antibiotics that are used in a chronic manner. Ultimately, this approach allows one to explore the implications of critical factors on treatment response and address critical questions regarding the experimental protocol before the actual study is conducted.

Results from Phase 2 and 3 trials have been traditionally reported without linking treatment outcome with individual drug exposure. However, availability of such data could explain variability in response and hence provide insight into whether any unsuccessful trial outcome might be attributed to underexposure to the drugs, rather than the novel regimen truly being inferior to the standard of care. Considering the cost and burden of Phase 2 and 3 trials, the integration of pharmacokinetics to efficacy trials should become a mandatory component of clinical protocols. Model-informed designs can be implemented that require sparse pharmacokinetic sampling, yielding accurate and precise estimation drug exposure in

individual patients **(28)**. A PKPD analysis can subsequently be performed to evaluate the relationship between drug exposure and clinical response.

Another important aspect regarding the evaluation of clinical response is the lack of consensus regarding the relevance of different endpoints in clinical trials (e.g. colony forming unit count vs. time to positivity). The concurrent use of different measures and regimen has made the comparison of historical and modern clinical trials incredibly challenging **(29)**. Rather than neglecting historical data, *in silico* models can be used to characterise the relationship between different measures of bacterial load **(30)**. The availability of such models will enable researchers to utilize as much existing data as possible to inform decision-making in TB drug development in a more robust manner.

Challenges for the implementation of a model-informed approach at candidate selection

The success of the proposed model-informed approach depends on the availability of suitable experimental data for the development of robust *in silico* models. This requirement is not trivial, in that most experimental protocols may only provide insight into the underlying PKPD relationships. These limitations are often determined by costs and time constraints. However, even when full PKPD relationships are characterised, discrepancies between animal models still pose a major challenge in extrapolating model predictions into clinical doses. Difference in bacterial strain (e.g. H37Rv *versus* Erdman), pathology (e.g. absence *versus* presence of necrotic lesions) or treatment condition (e.g. onset and duration of treatment) can yield significantly different PKPD parameters and hence varying predictions of the clinical dose.

Efforts are being made within PreDiCT-TB to overcome some of these challenges. The consortium has identified a range of *in vitro* and *in vivo* models and performed a range of experiments to compare the differences in PKPD relationship of various anti-TB regimens. Even though the current clinical regimens with isoniazid, rifampicin, ethambutol and pyrazinamide are not truly optimised, evidence of differences in the pharmacokinetics and pharmacodynamics of standard drugs across experimental models will provide insight into the sensitivity and specificity of these models to detect bactericidal, bacteriostatic and sterilising activity of the compounds currently used in humans.

Challenges for the implementation of a model-informed approach in clinical drug development

Most of the known issues for the clinical development of anti-tuberculosis agents cannot be overcome by PreDiCT-TB alone. First, variability in pharmacokinetics continues to be overlooked. Collection of individual drug exposure is not included as a standard procedure in clinical protocols and blood sampling may not even be feasible in high-burden countries where most Phase III TB trials are performed. In addition, even if individual PKPD data are collected, such as sputum conversion, information from single measurement at the time of relapse will be insufficient to allow the development of predictive models for the detection of relapse. In addition to further understanding of the underlying biological mechanisms of relapse, it is critical to obtain repeated microbiological data during treatment and follow up. From a drug development perspective, what seems to become clear from EBA studies is that information on early bactericidal activity may not be suitable descriptor of the processes associated with relapse. Another important limitation of EBA studies is that PKPD relationship

based on drug levels in plasma may not describe tissue exposure. Similarly, viable colony forming unit count in sputum may not represent the whole Mtb population in the human lung.

Despite such limitations, the opportunity to replace the empirical basis upon which doses are selected will represent an important advancement for therapeutics with novel anti-tuberculosis drugs. Last but not least, the consortium has managed to collate data from historical studies, creating a pool of individual patient level data which will facilitate the evaluation of the proposed framework for drug combinations.

Consequences for regulatory approval

Clearly, translation of the advancements obtained so far with regard to our increased understanding of the pathophysiology of infection by *M. tuberculosis* and improved knowledge of drug disposition and PKPD properties in tissues and target organs demands more than just the effective implementation of the MID3 concepts highlighted above. Regulatory acceptance and guidance needs to evolve as to ensure that lessons from this growing field are embedded into the drug approval process. A pro-active attitude by regulatory authorities has been observed in the last few years, in that a concept paper and new guidance have been issued, which focus on the development of entirely new regimens to treat TB, rather than focusing on single medicines.

Recently, the European Medicines Agency (EMA) opened a consultation for updating the guideline on the evaluation of medicinal products indicated for treatment of bacterial

infections **(31)**. Whereas the use of *in vitro* pharmacodynamic models such a the hollow fibre system have been endorsed for dose selection early on in the development programme, further insight from translational pharmacology and clinical trial simulations may play an important role in minimising the extent of dose- and/or regimen-finding clinical trials. Therefore, to be effective the new guidance should establish the mechanisms by which novel approaches for data generation and integration will be considered in future regulatory submissions. In this respect, a dialogue between public-private initiatives partnerships and regulatory agencies is timely and critical. Most importantly, regulators and experts need to weigh the importance of alternative endpoints and study designs for the approval of new medicines or combinations of medicines along with the role of biomarkers to predict the efficacy and effectiveness of alternative regimens during clinical development.

Conclusion

Improved efficiency in the development of drug combinations is urgently needed for the advancement of new treatments for tuberculosis. PreDiCT-TB has been created to overcome some of the critical gaps in early drug development and revolutionise the way evidence is generated and integrated to support the progression of candidate molecules into humans. The implementation of a model-informed approach to the design, analysis and interpretation of experimental data during preclinical phases of development will provide a more robust basis for the selection of suitable combinations and translate the appropriate dosing regimens for first time use in patients. In conjunction with clinical trial simulations, PreDiCT-TB expects to demonstrate the relevance of more informative clinical trial designs and offer regulatory

agencies a stronger scientific basis for the approval of treatments in a therapeutic area that has remained neglected for the last four decades.

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Conflict of interests

The authors declare that they have no competing interests.

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Table and figure legends:

Table 1. Overview of recommendations of how model-based approach can be used to address the current gaps in various stage of tuberculosis drug development.

Figure 1. Diagram describing the individual components of the integrated PKPD/disease modelling and simulation framework. The disease model encompasses the natural growth and elimination rate of Mtb in the absence of antibiotics. The drug model characterise the PK and PKPD properties as well as any covariate effects on the disposition or pharmacodynamics of the drug. In addition to the disease and drug components, a trial model is used to assess treatment performance in the context of a clinical trial protocol. Among other factors, a trial model allows the assessment of the impact of drop-outs, inclusion/exclusion criteria or compliance on trial outcome. Adapted from Gobburu and Lesko **(18)**.

Figure 2. A schematic overview of how PKPD/disease modelling and simulation framework can be applied to translate preclinical findings and identify the appropriate doses and dosing regimens for first time use in patients from preclinical experiments. Assuming the availability of data supporting the characterisation of dose/exposure-response relationship *in vitro* and *in vivo* (**left column**), *in silico* models can be developed that characterise the pharmacokinetic and pharmacokinetic-pharmacodynamic properties of the drug combinations of interest (**middle column**). After correcting for the interspecies differences in physiology and/or physiochemical properties, parameter estimates can subsequently be used to either scale

preclinical findings to humans or to facilitate the translation of drug effects taking into account differences between experimental and clinical conditions. Clinical trial simulations can be performed to inform the range of doses of each antibiotic that is expected to yield exposure levels (shaded green area) that are associated with the desired effect (dashed line) in preclinical experiments (**right column**).