ABSTRACTS
Abstract: O_1

Population PK/PD modeling

A model-based analysis to describe bedaquiline’s exposure-response relationship and predict the impact of drug-drug interactions

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Background: The efficacy of bedaquiline in treatment of MDR-TB has been demonstrated with time to sputum culture conversion (TSCC) and month 30 cure-rates, but no relationship between bedaquiline exposure and efficacy has been identified. We aimed to characterize this relationship by modeling serial measures of mycobacterial load, and utilize the model to evaluate the potential impact of known pharmacokinetic drug-drug interactions.

Methods: Quantitative mycobacterial load data (time to positivity [TTP] in mycobacterial growth incubator tubes [MGIT]) were obtained from a published Phase Ib study investigating the addition of either placebo or bedaquiline to an optimized background regimen in treatment of drug-resistant TB. Bedaquiline was dosed at 400mg QD the first 2 weeks, thereafter 200mg 3 times weekly. The study was conducted in accordance with Good Clinical Practice standards and received ethical approval from appropriate authorities.

The dataset used for model building included 5833 culture results (56.6% positive) from sputum samples collected during the first 20 treatment weeks in 189 individuals. Nonlinear mixed-effects models were developed in NONMEM7.3. Individual bedaquiline exposures were obtained from a separate pharmacokinetic model. The clinical importance of covariates, quantified by changes in TSCC and the proportion without sputum culture conversion at week 20 (noSCCw20), was assessed through simulations. Furthermore, the impact of coadministration of ritonavir-boosted lopinavir, efavirenz and rifampicin was investigated.

Results: The final model included three simultaneously fitted components: a longitudinal representation of mycobacterial load in patients over time after start of treatment, a model describing the probability of bacterial presence in a sputum sample, and a logistic growth-model characterizing mycobacteria in the MGIT system linked to the hazard in a time-to-event model for observed TTP. The joint model described the data well and a posterior predictive check demonstrated that TSCC was well predicted in both study arms.

Bedaquiline exposure quantified dynamically by weekly average concentration was found to significantly affect the half-life describing the decline in mycobacterial load. The estimated EC50 was 1.42 µg/mL (95%CI 1.02-1.99) which is higher than the typical observed average concentration in the continuation phase, but falls within the observed range of exposures. Median TSCC/noSCCw20 was predicted to 6 week/6.6% for MDR-TB patients with double the average exposure compared to 11 weeks/17% for those with half the average exposure (both exposure-levels within observed range). Patients with (pre-)extensively drug-resistant TB generally cleared mycobacteria 28% (95%CI 8.9-49) slower than patients with only rifampicin- and isoniazid resistance, typically resulting in 50-71% relative increase in noSCCw20. Baseline TTP was also found to be a significant covariate.

Bedaquiline exposure is expected to increase 13-98% during coadministration with lopinavir/ritonavir, decrease 16-47% with efavirenz, and decrease 40-76% with rifampicin, over the time-course of bedaquiline-treatment. For MDR-TB patients with average baseline mycobacterial load, the predicted relative changes in noSCCw20 were -32%, +29% and +64%, respectively.

Conclusion: The presented model provides the first characterization of an exposure-response relationship for bedaquiline and shows that increasing bedaquiline levels lead to faster mycobacterial response. The model can inform optimization of novel anti-TB regimens, including application in HIV-coinfected patients on interacting anti-retroviral drugs.

No conflict of interest
Abstract: O_2

Population PK/PD modeling

Population Pharmacokinetics of AZD5847 in Adults with Pulmonary Tuberculosis

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Background: AZD5847 is an oxazolidinone derivative being tested for the treatment of tuberculosis (TB). A phase II trial to evaluate its pharmacokinetics and early bactericidal activity in adults with pulmonary TB was completed recently. We developed a population pharmacokinetic (PK) model for AZD5847 using data from patients in this phase 2 study.

Methods: The study included 60 adults with newly-diagnosed, drug-susceptible TB. Patients were randomized to 4 arms - 500 mg once daily, 500 mg twice daily, 800 mg twice daily or 1200 mg once daily. PK sampling was done on day 1 and 14. Blood samples were collected at 0, 1, 2, 3, 4, 5, 6, 8, 12, 13, 15, 16, 17, 18, 20 and 24 hours.

Results: A total of 1723 samples were used for the analysis. A two compartment model with linear elimination and Tlag for absorption adequately described the data. AZD5847 showed non-linear absorption likely due to saturable absorption. Bioavailability started to decrease at the 800 mg daily dose and was 67% at the 1200 mg dose. Model parameters were Tlag (absorption lag phase), Ka (absorption rate constant), Cl (total body clearance), V1 (volume of distribution, central compartment), Q (inter-compartmental clearance) and V2 (volume of distribution, peripheral compartment). Typical values (relative standard error %) for Tlag, Ka, Cl, V1, Q and V2 were 0.27 hours (18%), 0.38 hour⁻¹ (9%), 7.96 L/hour (3%), 43.3 L (7%), 8.9 L/hour (13%) and 31.9 L (9%). The coefficient of variation (relative standard error %) for Tlag, Ka, Cl, V1, Q and V2 were 68.6% (22%), 21.6% (19%), 22% (10%), 14.9% (36%), 47.1% (28%), 55.6% (13%). The predicted average fAUC/MIC for AZD5847 following an 800 BID dose is 20 if the MIC = 1 ug/ml and 10 if the MIC = 2 ug/ml.

Conclusion: AZD5847 shows biphasic elimination. Absorption of AZD5847 is nonlinear and administering doses above 800 mg might not be beneficial. In a mouse model a minimum fAUC/MIC > 20 was required for bactericidal activity. This could help explain the limited bactericidal activity observed in the phase II study. Given the saturable absorption of AZD5847, it may be difficult to achieve favorable PK/PD targets in patients with TB.

No conflict of interest
Abstract: O_3

Population PK/PD modeling

Pharmacokinetic Modeling and Simulation of the Interaction between Moxifloxacin and Rifapentine in Healthy Volunteers

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Background: Moxifloxacin and rifapentine combination regimens are currently being investigated as shorter, safer, and more effective tuberculosis treatment strategies than the standard 6-month regimen. Rifapentine, an inducer of moxifloxacin metabolizing enzymes and transporters, may decrease moxifloxacin concentrations leading to reduced treatment efficacy or emergence of drug resistance. In this study, data from a pharmacokinetic (PK) study of healthy volunteers was used to develop a moxifloxacin PK model to evaluate the PK interaction between rifapentine and moxifloxacin. Simulations were then employed to assess the fraction of subjects above the suggested threshold for the moxifloxacin unbound AUC to minimum inhibitory concentration (fAUC/MIC) ratio, following co-administrations of 400, 600, or 800 mg moxifloxacin with 600 or 1200 mg rifapentine daily.

Methods: Fourteen healthy volunteers in a multiple-dose, two-period, sequential design study, received 400 mg moxifloxacin daily for four days, followed by two weeks of 400 mg moxifloxacin daily with 900 mg rifapentine thrice weekly. Moxifloxacin PK analysis were performed on Day 4 and Day 19 and rifapentine PK analysis were performed on Day 5 and Day 19. Model building was conducted using the NONMEM software. One- and two-compartment models with linear absorption, absorption lag times, and absorption transit compartments were evaluated. Non-linear and linear pharmacodynamic effect models were adapted to characterize the relationship between the observed rifapentine plasma concentration and the elimination rate of moxifloxacin. Model selection was achieved by the use of the objective function value and graphical analysis of the predictions. Statistical assessment between nested models were based on the likelihood test, assuming the objective function values are X² distributed. Simulations were performed using a composition of the developed moxifloxacin model and a rifapentine model developed in our lab for this healthy volunteer study. For the calculation of fAUC/MIC ratios, moxifloxacin was assumed to have an unbound fraction of 0.30 and minimum inhibitory

concentration of 0.5 mg/mL.

Results/Conclusions: Moxifloxacin and rifapentine PK data were best fit using one-compartment models with absorption transit compartments. The final rifapentine model included a semi-mechanistic auto-induction model. On the other hand, moxifloxacin data did not support the inclusion of an enzyme turnover model. Instead, a nonlinear relationship was modeled between rifapentine concentrations and moxifloxacin elimination rate. Simulations showed that once daily administrations of 400 mg moxifloxacin with 600 or 1200 mg rifapentine resulted in 37 and 49% of subjects encountering fAUC/MIC ratios below the minimum ratio required for suppression of drug resistance in humans. This was significantly higher than the 19% observed when moxifloxacin was administered alone. Increasing the moxifloxacin dose to 600 mg while keeping rifapentine doses at 600 and 1200 mg resulted in 10 and 16% of subjects below the minimum fAUC/MIC ratio. Furthermore, doubling the moxifloxacin dose to 800 mg resulted in 2 and 4% of subjects below the minimum fAUC/MIC ratio. These results suggest that a 400 mg daily dose of moxifloxacin co-administered with daily doses of rifapentine may result in reduced clinical efficacy due to the low moxifloxacin exposure. Higher moxifloxacin dosage should be considered. However, tolerability and toxicity of these high doses require further evaluation.

No conflict of interest
Abstract: O_4

Population PK/PD modeling

Population pharmacokinetic modeling to assess the non-linear increase in exposure following increasing doses of rifampicin

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Introduction: Accumulating evidence suggests that increasing the dose of rifampicin may reduce treatment duration for tuberculosis. In the recent multiple dose rising trial, PanACEA HIGHRIF 1, rifampicin was well tolerated at 40 mg/kg daily compared to the standard dose of 10 mg/kg. However, unexpectedly high exposures were observed at the higher doses. Our objective was to characterize the non-linear exposure in addition to auto-induction using non-linear mixed effects modeling in order to advice in optimizing the rifampicin dose.

Materials & Methods: Data consisted of plasma pharmacokinetic samples from 83 pulmonary tuberculosis patients given daily rifampicin of 10 (reference arm, n=8), 20, 25, 30, 35 or 40 (n=15/arm) mg/kg for 14 days, as monotherapy for 7 days and combined with isoniazid, pyrazinamide and ethambutol for the following 7 days. Blood samples were drawn at days 7 and 14 with rich sampling between 0 and 24 hours. Data were analysed using nonlinear mixed effects modeling in NONMEM 7.3. The M3 method in NONMEM was used to handle observations below the limit of quantification. Allometric scaling of clearance and volume of distribution was investigated using different body size descriptors. Rifampicin auto-induction was accounted for by an enzyme turn-over model. Non-linearity in exposure was evaluated in clearance and bioavailability. Concentration-dependency was evaluated in clearance using linear and Michaelis-Menten relationships whereas dose-dependency was evaluated in bioavailability using linear and Emax relationships. Different absorption models were evaluated including first-order absorption with and without lag time as well as using an absorption transit compartment model. Inter-individual variability was explored in all parameters. Inter-occasion variability was explored in all parameters except the parameters relating to the auto-induction.

Results: The final population pharmacokinetic model, including a one-compartment distribution model, an absorption transit compartment model and a Michaelis-Menten relationship for the nonlinear concentration-dependent clearance, described exposure in all dose groups and at the two occasions (days 7 and 14). Clearance and volume of distribution were scaled using fat free mass only using fixed exponents of 0.75 and 1, respectively. There was a good agreement between non-compartmental analysis (NCA) metrics (Cmax and AUC0-24h) at the two occasions of observed concentrations and simulated concentrations (n=1000 trials) based on the final model.

Conclusion: Our population pharmacokinetic model described the exposure-dependent auto-induction and non-linear decrease in clearance of rifampicin at higher doses. This model could be used when designing future trials involving rifampicin at doses higher than the current standard. The model also opens the possibility of clinical trial simulations of even higher doses that might optimize the rifampicin dose further.

No conflict of interest
Abstract: O_5
Pharmacokinetics and Pharmacodynamics of Approved Drugs

Lung Tissue Concentrations of Pyrazinamide among Patients with Tuberculosis

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Background: Improved knowledge regarding tissue penetration of anti-tuberculosis (TB) drugs may help guide drug development and optimize drug dosing and management.

Methods: Patients with pulmonary tuberculosis undergoing adjunctive surgery were enrolled in Tbilisi, Georgia. Serum was obtained at 0, 1, 4, and 8 hours and at time of surgical resection to measure pyrazinamide concentrations using LC-MS-MS. Free serum concentrations were calculated by multiplying total serum concentrations times expected fraction unbound (0.85). After surgery, microdialysis was performed using the ex vivo tissue samples and drug concentrations were measured in collected dialysate fluid. Noncompartmental analysis was performed and a tissue to serum concentration ratio was calculated. All resected tissue samples were processed for acid-fast bacillus (AFB) smear and culture and had pathology examination performed, including pH measurement. When available, preoperative chest computed topography (CT) scans were reviewed by two radiologists. The association of radiology and pathology characteristics on drug penetration was examined.

Results: Ten patients receiving pyrazinamide and undergoing surgical resection were enrolled. Eight of ten were male; median age was 30 years, body mass index 19.6 kg/m2, and creatinine clearance 91 ml/min. Most were receiving a dose of 1600 mg (n=8), for a median of 363 days; median weight based dose was 24.7 mg/kg. Chest CT scans revealed the predominant lung lesion to be either cavitary (n=5), mass-like (n=3), or a consolidation (n=2). On pathology examination, all resected tissue samples had necrosis ranging from 1-3 (scale 0-3) and three had a tissue pH of 7.2 with the remaining having a pH of ≤ 5.5. Eight of ten patients had tissue samples stain positive for AFB organisms 2 patients had tissue cultures positive for M. tuberculosis (pH of 7.0 and 7.2). The large majority of patients (90%) had Cmax within the usual range of 20-60 µg/ml; the median free serum concentration at time of surgical resection was 27.87 µg/ml. Nine of ten patients had tissue concentrations of pyrazinamide available; median lung tissue concentration was 20.96 µg/ml (range 13.95-40.17). In comparison to the free serum concentration of pyrazinamide at the time of surgical resection, the median tissue/serum pyrazinamide concentration ratio was 0.77, with a range of 0.54 to 0.93. While no association with tissue pyrazinamide concentrations and type of lesion per radiology was identified, there was a significant inverse correlation between tissue pyrazinamide concentrations and the amount of necrosis (r=-0.66, p=0.04) and AFB organisms (r=-0.75, p=0.01) identified by pathological examination.

Conclusions: We found good penetration of pyrazinamide into TB diseased pulmonary tissue among patients with a variety of radiological lesion types. All patients with TB had a ≥ 0.50 tissue/serum pyrazinamide ratio. Absolute tissue concentrations were lower in patients with lesions characterized by higher levels of necrosis and AFB positive organisms. Our pH tissue results are the first recorded among TB patients in > 50 years and revealed most lesions had a low pH which is conducive to the activation of pyrazinamide. The good tissue penetration of pyrazinamide highlights its importance in TB treatment, both in drug susceptible and MDR anti-TB treatment regimens.

No conflict of interest
Abstract: O_6

Pharmacokinetics and Pharmacodynamics of Approved Drugs

Early interventions for diabetes related tuberculosis hasten sputum microbiological clearance in Virginia, USA

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Background: Diabetes complicates tuberculosis (TB) treatment including a prolonged time to sputum culture conversion to negative growth. Since 2013 in Virginia, interventions early in the treatment course have used therapeutic drug monitoring (TDM) and dose correction for isoniazid and rifampin after 2 weeks of TB treatment in patients with diabetes along with nurse manager initiated diabetes education and linkage to care.

Materials & Methods: A retrospective cohort study of the state TB registry was performed for patients initiating drug-susceptible pulmonary TB treatment in pre intervention group (2009-2010) and post intervention group (2013-2014). Diabetes patients undergoing early TDM in the pre and post-intervention groups were matched for age, gender, chest imaging and sputum smear status to compare time to sputum culture conversion and other clinical outcomes.

Results: 539 patients in the pre-intervention group and 391 patients in the post-intervention group. Diabetes was present in 64 (12%) in the pre-intervention group and 66 (17%) in the post intervention group with mean age of 60±18 and 63±13 years respectively. 26 diabetes patients were able to be matched in each group. Mean time to sputum culture conversion in the post intervention group was 42 days [±22] compared to pre intervention group of 62 days [±31] (p=0.01), while 13 (50%) in the pre intervention group converted before 2 months compared to 21 (80%) in the post intervention group (p=0.04).

Conclusions: Early interventions for diabetes related TB may hasten sputum culture conversion in the programmatic setting.

No conflict of interest
Abstract: O_7

TB Treatment in Special Populations

Sub-therapeutic concentrations of anti-tuberculosis drugs in children when treated according to Indian dosing recommendation

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Introduction: First line dose recommendations of anti-tuberculosis (TB) treatment in children are based on pharmacokinetic (PK) studies in adults, yet new evidence reveals that small children are often underexposed, which may lead to poor clinical outcomes. This work aimed to (i) characterize the PK of isoniazid (INH), rifampicin (RIF) and pyrazinamide (PZA) in Indian children undergoing thrice weekly dosing, (ii) relate plasma exposure of INH, RMP and PZA to treatment outcomes and (iii) evaluate current Indian pediatric dose recommendations for the treatment of drug-sensitive TB Indian children.

Materials & Methods: The clinical data were pooled from two studies in 161 Indian children (1–15 y, 6–44 kg) diagnosed with drug sensitive TB, 84 of whom had HIV coinfection and anti-retroviral therapy. Plasma concentrations of INH, RIF and PZA were measured at 0, 2, 4, 6 and 8 h following dose intake. Individual drug exposure for the three drugs were predicted using nonlinear mixed-effects models. The effect of body weight (allometry), nutritional status (z-scores) and HIV related covariates were tested on clearance, volume of distribution, bioavailability and absorption delay. The demographic covariates, z-scores, TB-type, HIV related covariates and model predicted plasmatic exposure (AUC) for each drug were evaluated as predictor of treatment outcome (where unfavorable outcome was defined as treatment failure or death) using a logistic regression model. Finally, the RIF dose required to achieve 95% of favorable outcome was calculated from the model for each patient subgroups and compared against the current Indian pediatric dosing recommendations.

Results: The PK of INH, RIF and PZA was linear over the studied dose range and all displayed delayed absorption. The distribution of RIF and PZA was monophasic whereas INH followed a biphasic distribution. The estimated clearances for INH and RIF were significantly lower than reported values for similar studies in South African children. Furthermore, the predictions for all three compounds were significantly improved when bioavailability was allometrically scaled to body weight. HIV coinfection influenced the bioavailability of INH (-20%) and RIF (-42%) as well as the clearance (+32%) of RIF. RIF exposure was the only independent predictor of treatment outcome. The highest incidence of poor treatment outcome was associated with RIF underexposure in HIV+ and small (6–10 kg) children. To achieve 95% of favorable outcome, the model predicted that mg/kg doses should be adjusted for the different patient subgroups, with the highest predicted doses for small and HIV+ children. For all patient subgroups, the required doses were significantly higher than the current Indian dosing recommendations.

Conclusion: The developed model revealed significantly lower exposures of INH, RIF and PZA in small children and of INH and RIF in HIV+ children when treated according to current thrice-weekly Indian dosing recommendations. The underexposure to RIF in these subgroups was associated with an increased probability of poor treatment outcome. The model prediction highlights the need for revised pediatric guidelines with an increased dosing regimen especially for small and HIV+ children.

No conflict of interest
Abstract: O_8

Population PK/PD modeling

A Need for altering Tuberculosis Dosing Regimens for patients with HIV-associated Tuberculous Meningitis


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Introduction: Anti-tuberculosis (anti-TB) drug pharmacokinetics (PK) are likely to influence outcome in patients with tuberculous meningitis (TBM), but its impact has never been studied in HIV-infected TBM patients.

Materials & Methods: A randomised, double-blind, placebo-controlled trial of immediate (at randomisation) versus deferred initiation (at 8 weeks) of antiretroviral therapy (ART) was conducted in HIV-infected patients with TBM. All subjects were treated with standard first-line anti-TB therapy. PK modelling was performed to assess drug exposure levels in plasma and cerebrospinal fluid (CSF) and their relationship to clinical outcome at 12 months.

Results: The HIV/TBM cohort displayed low CSF and systemic exposures to rifampicin compared to previously reported TB cohorts. Rifampicin concentrations in the CSF in this cohort were below the minimum inhibitory concentration (MIC) for most clinical strains of M. tuberculosis. Elevated CSF concentrations of pyrazinamide were strongly correlated with increased mortality, and increased frequency of neurological events. No clinically significant interactions between anti-TB therapy and time of ART initiation were found.

Conclusions: These findings suggest that current anti-TB dosage regimens in this population may put the patient at risk of treatment failure from inadequate rifampicin exposure, whilst increasing the risk of adverse events related to high CNS levels of pyrazinamide. We also found that deferring ART initiation in HIV/TBM patients had no effect on systemic or CNS anti-TB drug exposure and no clinical benefit.

No conflict of interest
Abstract: O_9
Pharmacokinetics and Pharmacodynamics of Approved Drugs

Development of a novel multi-compartment granuloma model to predict local drug distribution and its impact on pharmacodynamics and disease progression in tuberculosis.

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Introduction: One of the hallmarks of pulmonary tuberculosis (TB) is the formation of granulomas, heterogeneous lesions composed of macrophage and neutrophil rich peripheral regions and a necrotic core, in the lungs of the infected host. Anti-TB drugs must penetrate these lesions to exert their effects. This work aimed to extend a permeability-limited lung model [1] to describe drug disposition within a tuberculosis granuloma and to incorporate a disease progression model that describes the growth of the granuloma and the pharmacodynamic effect of locally-acting drugs on bacteria located within different lesions of the granuloma.

Methods: A permeability-limited lung model was extended with the addition of a novel multi-compartment granuloma model consisting of three layers: the well vascularised cellular rim, the outer caseum and the inner caseum compartments. The rim was further sub-divided into mass, interstitial fluid (ISF) and blood compartments. Granuloma growth and disease progression in active and latent tuberculosis was modelled based on work published previously [2]. The volume of the rim mass compartment was defined by the total number of macrophages from the disease progression model and drug effects are incorporated as a local concentration dependent kill rate for bacteria localised to different compartments of the granuloma. The model has been implemented in Simcyp V16, with the disease progression model implemented via a Lua script to allow the user the flexibility to customise the model.

Results: Local free drug concentration within different granuloma compartments is dependent on the interplay between several factors including free drug concentration in the plasma and lung tissue of the simulated individual, passive permeability between granuloma compartments and binding within different compartments of the granuloma model. Local free drug concentration significantly impacts on the rate of killing of bacteria within different granuloma compartments and hence the predicted response to treatment.

Conclusions: The multi-compartment granuloma model provides a framework for investigating the impact of inter-individual variability in drug pharmacokinetics and local drug concentration on the killing of M. tuberculosis sub-populations. Ongoing work aims to validate the model predictions for anti-TB drugs and treatment regimens.

References:

Conflict of interest financial relationship(s): R.H.R., L.G., J.W., B.G.S., A.B., I.G. and M.J. are all employees of Simcyp (a Certara Company). D.H. is an employee of Certara USA.
Abstract: O_10

Pharmacokinetics and Pharmacodynamics of Approved Drugs

Application Of A Multi-Compartment Permeability-Limited Lung Model To Predict Lung Concentrations Of Moxifloxacin In Virtual Human Subjects

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Introduction: Tuberculosis remains a major global health problem [1]. Current therapies for pulmonary TB use combinations of orally dosed drugs to achieve adequate concentrations in the lungs of infected individuals to gain therapeutic benefit. Moxifloxacin, a fluoroquinolone antibiotic has been used in conjunction with standard therapy to treat pulmonary TB [2].

Materials and Methods: A whole body PBPK model was constructed for moxifloxacin with the lung (airways and lobes) represented by a total of 7 permeability limited compartments (Simcyp simulator, V14R1). Each of the compartments was divided into sub-compartments representing the pulmonary capillary blood, pulmonary tissue mass, epithelial lining fluid (ELF) and alveolar air. The distribution of moxifloxacin within the compartments of the lung PBPK model was predicted using in vitro permeability and P-glycoprotein (P-gp) kinetic data from Calu-3 cells [3].

Results: The in vitro intrinsic clearance of moxifloxacin by P-gp (31.6 μl/min) was estimated using the SIVA toolkit (V1.0, Simcyp Ltd, Sheffield, UK) and was extrapolated to the in vivo situation accounting for differences in surface area. The concentrations predicted to occur in the ELF and lung tissue and the ratios of these concentrations to the plasma concentration were compared to reported values from human clinical studies. Following oral dosing with moxifloxacin (400 mg) lung: plasma ratios of 1.7 – 4.4 and ELF: plasma ratios of 3.5 – 7.4 have been reported [4-6]. Model performance was verified by comparison to the reported plasma time-concentrations of moxifloxacin at doses of 100-600mg. The pharmacokinetics of moxifloxacin are linear over this dose range. The predicted clearance for a 400mg oral dose 16.1 ±3.0 L/h, plasma half-life 12.3 ±3.24 h and urinary excretion 12-26% were within the range of reported values (13.2-17.6L/h, 10.3-15.0 h, and 14.4-21.8%, respectively) [7]. Purely accounting for passive distribution processes in the lung led to a reasonable estimate for the lung tissue: plasma moxifloxacin concentration ratio (5.5) but under-predicted moxifloxacin concentration in ELF (ELF: plasma ratio 0.6). Using in vitro data to describe the effect of P-gp transport of moxifloxacin from lung tissue to ELF increased this ratio to 2.3-4.9, but this still underpredicted the observed concentration ratios. A sensitivity analysis was undertaken to examine the impact of increasing the P-gp apical efflux intrinsic clearance on the ELF:plasma ratio.

Conclusions: Good predictions of the ELF:plasma ratio (4.0-9.1) were seen using a 2-fold higher P-gp intrinsic clearance suggesting further refinement of the in vitro: in vivo extrapolation procedure is needed. A possible reason for the discrepancy between the in vitro and in vivo situation include the difference in P-gp expression/activity in the in vitro system and in vivo.

This poster was previously presented at the 20th North American ISSX Meeting, Orlando, Florida, USA, Oct 2015.

References:

Conflict of interest financial relationship(s): O.J.D.H, N.P., H.J.B., S.N. I.G and M.J. are employed by Simcyp (a Certara company). D.H. is employed by Certara USA.
Abstract: O_11

Pharmacokinetics and Pharmacodynamics of Approved Drugs

A translational modelling and simulations approach to exploit pre-clinical tuberculosis data

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Introduction: Development of novel therapeutic drugs and therapeutic regimens in tuberculosis research is time-consuming and resource-intense. In order to exploit pre-clinical in vitro information on tuberculosis drugs utmost, the present study aimed at defining and evaluating a translational approach using the recently developed Multistate Tuberculosis Pharmacometric model (MTP model, Clewe et al. JAC 2016) for prediction across in vitro systems, to animals and to humans, using rifampicin (RIF) as model drug.

Methods: For translational prediction, estimates from a static in vitro system combining both log- and stationary phase RIF effects were used as origin system for translation. The MTP model was extended to capture (i) persistent drug effects originating from post-antibiotic effect studies, (ii) differences in mycobacterial susceptibility by a MIC-based scaling approach considering MIC uncertainty and/or MIC distribution (e.g. from EUCAST), (iii) growth properties of mycobacteria in the target system (i.e. log- or stationary phase, carrying capacity), (iv) protein binding and plasma/target site exposure (if applicable). The extended MTP model was used to predict in vitro hollow-fiber experiments, a murine dose fractionation study for determination of PK-PD indices and a 14 day clinical trial of RIF 10 mg/kg daily to determine early bactericidal activity (EBA). R software (version 3.2.1) was used for simulation and data processing.

Results: The extended MTP model successfully predicted hollow-fiber experiments for RIF. The result of a murine PK-PD study was also well predicted and the PK-PD indices AUC/MIC and Cmax/MIC were correctly identified. Using clinical trial simulations, the PK-MTP model predicted mean EBA0-2days of 0.160 log CFU/mL/day [90% prediction interval (PI90): 0.074-0.364] and mean EBA0-14days to 0.143 log CFU/mL/day [PI90: 0.055-0.251], which was well in agreement with the observed clinical result for RIF from several clinical trials.

Conclusion: The MTP model was successfully applied for translational predictions from in vitro time-kill experiments to hollow-fiber, animal and clinical studies for determination of EBA. The present study sets the basis for further systematic evaluation of translational predictions with further tuberculosis drugs and drug combinations.

No conflict of interest
Abstract: O_12

Pharmacokinetics and Pharmacodynamics of Approved Drugs

The relationship between pyrazinamide pharmacokinetics (PK) and microbiologic outcomes in patients with pulmonary TB receiving standard- or high-dose rifampicin: PK/PD results from TBTC trials 27 and 28 and PanACEA MAMS

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Background: Pyrazinamide (Z) has potent sterilizing activity against Mycobacterium tuberculosis and is a major contributor to successful treatment, and its use in modern regimens has allowed for tuberculosis treatment shortening. The relationship between Z pharmacokinetics (PK) and treatment outcomes as well as adverse effects remains poorly defined and may depend on companion drugs in the regimen. Using data from Tuberculosis Trials Consortium (TBTC) Studies 27 and 28 and the recent PanACEA MAMS trial we assessed the association between Z PK and microbiologic activity when Z is given with standard-dose or high-dose rifampicin (R) as part of multidrug regimens.

Materials and Methods: All studies involved participants with sputum smear-positive drug-sensitive pulmonary TB. TBTC Study 27 was an 8-week study of isoniazid, rifampicin, pyrazinamide, and moxifloxacin (HRZM) versus HRZ+ethambutol (HRZE). TBTC 28 evaluated MRZE vs. HRZE. In each study, Z was given at a dose of 20-25 mg/kg (1000-2000 mg), and R was dosed at 10 mg/kg (450 or 600mg). For 72 patients, PK samples were collected prior to, and 1, 2, 6, 12 and 24 hours post-dose at least 10 days into treatment. The minimum inhibitory concentration (MIC) for Z against patient isolates was measured using the BD BACTEC MGIT 320 system. Sputa for culture were collected bi-weekly. In PanACEA MAMS, a 12-week study, the arms were HR10ZQ, HR20ZQ, HR20ZM, HR35ZE, and HR10ZE (subscript indicates the mg/kg dose; Q is SQ-109). Z was given at a dose of 25-30 mg/kg (800-2000mg). PK sampling (10 samples/participant) was performed on Day 28. Sputa for culture were collected bi-weekly. Combined pharmacokinetic/pharmacodynamic (PK/PD) analysis was performed using all PK and microbiologic data in NONMEM, with time to culture conversion as the main outcome.

Results: In the TBTC studies, Z Cmax ranged between 15 and 55 mcg/mL. MIC ranged between 25 and 75 mcg/mL. Cmax was the parameter that correlated best with time to culture conversion (p=0.004). Proportion of patients with negative 2-month culture conversion ranged from an estimated 69% (95%CI: 63-76% at a Cmax of 15 mcg/mL) to 87% (05%CI: 76-94% at a Cmax of 55 mcg/mL). Combining data from all three trials, there was a clear inverse, steep exposure-response relationship between Z exposure or Cmax and time to negative culture that did not plateau. This was true for standard-dose R (e.g. Cmax of 10) and for high-dose R (e.g. Cmax of 30). Outcomes were best among those with both high R and Z exposures. Liver events were uncommon, and there was no discernible relationship between Z exposure and grade 3 events in limited analyses.

Conclusions: The microbiologic efficacy of Z increases with increasing exposure. This is true with regimens containing standard-dose or high-dose R, though the very best microbiologic responses are seen with high exposures to both R and Z. This analysis provides supportive data for a treatment-shortening trial involving high-dose R and higher-dose Z. The safety of such a treatment strategy remains to be explored.

No conflict of interest
Abstract: O_13

Population PK/PD modeling

Simulation of long-acting administration of antituberculosis agents using pharmacokinetic modelling

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Background: The efficacy of anti-tuberculosis (TB) treatment is defined by several factors including bacterial resistance and host immunological status. It is increasingly clear that poor adherence to anti-TB drugs can have a primary role in causing treatment failure. Poor adherence has been correlated with various factors including pill fatigue, side effects and social conditions associated with affected populations. Currently available anti-TB formulations necessitate regular dosing where poor adherence often results in higher rates of treatment failure. Long-acting (LA) injectable formulations can simplify drug administration, addressing problems related to adherence and have been successfully introduced in various disease areas such as contraceptives, anti-psychotics and antiretrovirals. The aim of this study was to simulate the pharmacokinetics (PK) of theoretical LA formulations for the anti-TB agents - rifapentine (RFP), delaminid (DLM) and bedaquiline (BDQ) using PK modelling.

Materials & Methods: Experimental and population PK data were integrated in a mathematical description of drug distribution using SimBiology® (version 5.1, MATLAB® 2013b, MathWorks Inc., Natick, MA, USA). Virtual individuals were simulated using a mathematical description of covariance between demographics and tissue size, blood flows and processes regulating drug distribution. The PK of RFP, DLM and BDQ were simulated for 200 individuals for each following standard oral dose and validated against available clinical data. Subsequently, theoretical intramuscular administration of a LA nanoformulation was simulated, optimizing depot release rate to maximize exposure over a month.

Results: The simulated PK parameters for the oral PK of RFP, DLM and BDQ were in agreement with previously published clinical data. The mean values of AUC were 349 vs 330 µg.h/ml, Cmax 21 vs 21.7 µg/ml and C24 8.1 vs. 7.6 µg/ml for RFP (10 mg/kg QID at steady state) administration. The simulated PK following intramuscular injection of a theoretical LA nanoformulation resulted in sustained plasma concentrations up to a month for all three anti-TB agents. RFP was characterized by a Cmax of 4.2 µg/ml and Ctrough of 0.86 µg/ml; DLM by a Cmax of 0.38 µg/ml and Ctrough of 0.08 µg/ml and BDQ by a Cmax of 2.11 µg/ml and Ctrough of 0.29 µg/ml.

Conclusion: The identification of suitable candidates for LA strategies is complex and based on several factors: drug formulation, toxicity, PK as well as pharmacodynamic characteristics. Based on their PK properties, RFP, DLM and BDQ are potential candidates for once-monthly injection, suggesting that these anti-TB agents could be reformulated into IM LA medicines if the technological complexities associated with reformulation can be overcome. These data may help inform the target product profiles for LA anti-TB reformulation strategies, providing a rational evaluation of the potential drug candidates.

No conflict of interest
Abstract: O_14

Drug Development and optimization: Approaches & Tools

High drug tolerance of Mycobacterium tuberculosis in caseum

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The eradication of tuberculosis (TB) requires antibiotics to reach bacterial populations sequestered in remote lesion compartments. In addition, TB drugs face a second challenge in these remote niches where stressful environmental conditions cause M. tuberculosis to enter a state of dormancy which makes these subpopulations especially resistant to antibiotic therapy.

There are several in vitro models aimed at generating drug-tolerant persisters by mimicking specific stress conditions, but the predictive value of these models remains unknown. Since the failure of tuberculosis treatment is largely associated with the presence and extent of cavitary disease, we aimed to accurately determine the potency of selected first- and second–line agents against non-replicating M. tuberculosis in cavity caseum obtained from infected rabbits.

Our results show that intra-caseum tuberculosis is significantly more resistant to antibiotics than actively replicating bacteria.

From a previous clinical study of TB drug penetration into human lung lesions, we modeled the concentrations of TB drugs in cavity caseum throughout the 24h dosing interval. Using estimated values of clearance, volume of distribution and the ratio of drugs entering cavity caseum from plasma, we simulated the average 24 hour drug concentration in the caseum compartment of 1000 individuals, to derive cavity-centric PK-PD parameters.

Only rifampicin and moxifloxacin proved potent against intra-caseum tuberculosis at concentrations that are clinically achievable in this compartment. Isoniazid, pyrazinamide, linezolid, kanamycin and clofazimine had little effect against this subpopulation.

To test the usefulness of nutrient- and oxygen–starved in vitro models of non-replication (the Loebel and Wayne models respectively) in predicting drug potency against caseum M. tuberculosis, we compared the minimum bactericidal concentrations (MBC) of these TB drugs in all three assays. Significant differences in susceptibility were observed for selected TB drugs, indicating that these in vitro assays can’t be substituted for the caseum MBC in drug discovery programs.

In summary, we have provided the first experimental evidence for the persistent bacilli theory. The caseum MBC assay is a useful tool for the accurate determination of drug potency against non-replicating M. tuberculosis from a clinically-relevant niche.

No conflict of interest
Abstract: O_15

Pharmacokinetics and Pharmacodynamics of Approved Drugs

Rifapentine plus Isoniazid Eradicates Mycobacterium tuberculosis among Rhesus Macaques with Latent TB Infection

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Introduction: Weekly rifapentine (RPT) and isoniazid (INH) given for 12 weeks is a CDC-recommended regimen for the treatment of latent TB infection (LTBI) in humans but there are no data on the use of this regimen in non-human primates (NHPs). Pharmacokinetic (PK) studies were carried out among NHPs (rhesus macaques) with LTBI treated with RPT/INH.

Materials & Methods: The Tulane Institutional Animal Care and Use Committee (IACUC) approved the study. Six NHPs were infected with Mycobacterium tuberculosis (CDC 1551) by aerosolization and determined to have LTBI based on a positive tuberculin skin test and interferon-γ release assay, a negative chest radiograph, and negative bronchoalveolar lavage culture. 18 weeks following infection, NHPs were randomized to weekly treatment (x 12 weeks) with RPT/INH (n=3) or no treatment (n=3). PK studies were performed at week 1 and 12 of treatment; 3 NHPs were dosed with 90 mg each rifapentine and isoniazid (15 mg/kg). All doses of RPT and INH were given orally in Gatorade when the PK studies were performed due to the need to anesthetize animals for the blood draws; on other weeks the medications were given with peanut butter. For PK studies, plasma samples were collected at 0, 2, 4, 6, 8, 12, 24, 48 and 72 hours post RPT/INH doses. Samples were stored at - 80°C until assayed at the University of Florida using a validated HPLC UV assay. The plasma standard curve for RPT ranged from 0.50 to 50 mcg/mL, while INH ranged from 0.40 to 20 mcg/mL. Phoenix v6.2 software was used for the non-compartmental analysis. Statistical tests were performed using JMP v10 (SAS Institute, Cary, NC USA).

Results: For INH, NHPs reached Cmax by 2 hours (similar to humans) but values were less than the typical human range of 9-15 mcg/ml. PK at 12 weeks showed very low INH values in 2 of 3 animals. For rifapentine, NHPs reached Cmax by 8 hours (similar to humans) but 4/6 values were less than the typical human range of at least 8 – 30 mcg/ml. RPT could be detected to 72 hours in all animals. Half-lives ranged from 12 to 50 hours, and generally were longer at week 12 of therapy compared to PK at week 1. Four weeks following completion of LTBI therapy (week 34 after infection), all NHPs were infected with SIV in an effort to precipitate TB disease progression. At necropsy (week 40 after infection), the 3 NHPs treated for LTBI were culture negative for Mtb while all 3 NHPs that were not treated for LTBI were culture positive for Mtb.

Conclusions: Treatment of LTBI with RPT/INH appears to eradicate Mtb infection in NHPs; preliminary data suggests that this may be a useful animal model for the study of LTBI. PK/PD studies carried out on RPT and INH suggest that the Tmax for these drugs in NHPs is similar to that seen in humans but levels were generally lower than those typically seen among humans.

No conflict of interest
Abstract: O_16

Drug Development and optimization: Approaches & Tools

Exploration of Non-Replicating Mycobacterium Tuberculosis In Vitro System Through Mathematical Modelling.

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Background: M. tuberculosis strain 18b, a member of the Beijing family, is a streptomycin (STR)-dependent mutant that enters a viable but non-replicating state in the absence of STR. The STR-dependent M. tuberculosis strain 18b can be used to evaluate drug efficacy in vitro in this non-replicating state (upon STR removal) by measuring luminescence of bacteria through a luciferase assay. A mathematical modelling approach can then be applied to describe the change bacterial luminescence over time under drug treatment and thus parameterise the efficacy of drugs to assess their overall potency against M. tuberculosis in this system, and then rank their efficacy in terms of model derived parameters.

Methods: a two stage analysis was developed for the analysis of the data.
Stage1- Profiles of luminescence values vs. time, at different drug concentrations, were used to estimate elimination rate constants (slope values in a mono exponential decay) under drug treatment.
Stage 2- Using the elimination rate constants it was possible to estimate an IC50 and Imax for the elimination rate constant as a function of drug concentration using an Imax response model:

\[ E = E_0 - \frac{(I_{\text{max}} \cdot [\text{Drug}]^\gamma)}{(IC_{50}^\gamma + [\text{Drug}]^\gamma)} \]

Where E represents the effect of the drug at different drug concentrations, in this case the elimination rate constant.

Results: A sample ranking table of the top 5 drugs ranked by IC50 regarding elimination rate constant is given below:

<table>
<thead>
<tr>
<th>Rank(IC50)</th>
<th>Drug</th>
<th>IC50</th>
<th>Imax</th>
<th>Imax/IC50</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Rifabutin (RFB)</td>
<td>0.004</td>
<td>0.282</td>
<td>6.79E+01</td>
</tr>
<tr>
<td>2</td>
<td>Rifapentin (RPT)</td>
<td>0.031</td>
<td>0.121</td>
<td>3.90E+00</td>
</tr>
<tr>
<td>3</td>
<td>Pretomanid (PA-824)</td>
<td>0.102</td>
<td>0.119</td>
<td>1.17E+00</td>
</tr>
<tr>
<td>4</td>
<td>Rifampicin (RIF)</td>
<td>0.189</td>
<td>0.105</td>
<td>5.58E-01</td>
</tr>
<tr>
<td>5</td>
<td>Sutezolid (PNU100480)</td>
<td>1.160</td>
<td>0.243</td>
<td>2.10E-01</td>
</tr>
</tbody>
</table>

Conclusions: This work is a further example of the use of mathematical modelling to parameterise and quantify drug efficacy to enable comparisons of relative efficacy. Specifically, compared to other in vitro models, the parameter estimates and rankings from this data can be said to reflect elimination of ‘dormant’ M. tuberculosis, and the IC50 the antibacterial potency of a therapy vs. ‘dormant’ M. tuberculosis, with rifamycins tending to show good efficacy.

No conflict of interest
Abstract: P_17

Pharmacokinetics and Pharmacodynamics of Approved Drugs

Isoniazid and levofloxacin pharmacokinetics and outcomes in a Russian cohort

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Introduction: In Irkutsk, Siberia, multidrug-resistant (MDR), pre extensively drug-resistant (pre-XDR) and extensively drug-resistant (XDR) tuberculosis (TB) are common and drive mortality in patients infected with human immunodeficiency virus (HIV). Isoniazid (INH) and levofloxacin (LFX) are commonly given in all forms of drug-resistant TB in Irkutsk, and high-dose INH is increasingly incorporated in short-course MDR regimens worldwide. Little is known about the pharmacokinetics of anti-TB medications in HIV infected patients in Russia.

Methods: Among consecutively enrolled HIV infected patients initiating anti-TB treatment at a referral hospital in Irkutsk, after 2 weeks of treatment, 2 and 6 hour plasma samples were collected for determination of estimated peak concentration (Cmax). Drug concentrations were determined utilizing a variety of analytic methods (U Florida), the data for INH and LFX reported here. Minimum inhibitory concentration (MIC) and determination of phenotypic drug resistance was completed onsite using the MYCOTB Sensititre plate. Potential drug activity was defined as a Cmax greater than individual isolate MIC. Patients were followed prospectively and treatment failure was defined as default or death while treatment success was defined as cure or treatment completion.

Results: 69 patients were enrolled and able to complete procedures, among whom there was significant variation in drug susceptibility patterns. Of the total isolates from each patient, 36 (52%) were DS-TB, 11 (15.9%) were MDR, 16 (23.1%) Pre-XDR, and 6 (8.7%) were XDR. Thirty-eight patients were treated with INH, all at high doses, median dose of 575 mg (IQR 500-600 mg). The median INH MIC was 2.0 (0.81-4.0). Among those with MDR, pre-XDR or XDR and both INH Cmax and MIC data, INH had activity in 8 (80%). Of those with INH activity, treatment success occurred in 6 (75%) compared to the 2(100%) without activity who both experienced treatment failure, p=0.05. The median INH Cmax/MIC, with exclusion of default, was 1.26 (0.00-2.52) and 1.77 (1.44-1.80) among those with treatment failure and success respectively.

Conclusion: Among consecutively enrolled HIV infected patients initiating anti-TB treatment at a referral hospital in Irkutsk, after 2 weeks of treatment, 2 and 6 hour plasma samples were collected for determination of estimated peak concentration (Cmax). Drug concentrations were determined utilizing a variety of analytic methods (U Florida), the data for INH and LFX reported here. Minimum inhibitory concentration (MIC) and determination of phenotypic drug resistance was completed onsite using the MYCOTB Sensititre plate. Potential drug activity was defined as a Cmax greater than individual isolate MIC. Patients were followed prospectively and treatment failure was defined as default or death while treatment success was defined as cure or treatment completion.

No conflict of interest
Abstract: P_18

Pharmacokinetics and Pharmacodynamics of Approved Drugs

Optimizing the Dose of Rifampin: Pharmacokinetic Results from the HIRIF Trial


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Background: Rifampin displays profound concentration-dependent killing of M. tuberculosis, which is not fully exploited by the standard 600 mg dose. This blinded, randomized trial compared 10, 15 and 20 mg/kg of rifampin delivered orally, 7 days per week for 8 weeks, at participating centers in Peru. Patients also received standard oral doses of isoniazid, pyrazinamide, and ethambutol, and a continuation phase of isoniazid 10 mg/kg/day and rifampin 10 mg/kg/day 3 days/week for 18 weeks.

Materials & Methods: The study protocol and informed consent documents were reviewed and approved by Institutional Review Boards at all participating institutions. Rifampin and placebo were provided by the Sanofi-Aventis Groupe. The study population included adults with newly diagnosed, previously untreated, smear positive (>2+) pulmonary tuberculosis. All study treatment doses were directly observed. After no fewer than 13 and no more than 56 (including 3 consecutive daily) doses of RIF, plasma samples were collected at 0, 2 and 6 hours post dose (sparse, 67%) or 0 hours plus sampling windows centered on 0.5, 1, 1.5, 2, 6 and 14 hours post dose (intensive, 33%). Samples were stored at -80°C until assayed at the University of Florida using a validated LC MS MS assay. The plasma standard curve for rifampin ranged from 0.05 to 50 mcg/mL. Phoenix v6.2 software was used for the non-compartmental analysis. Statistical tests were performed using JMP v10 (SAS Institute, Cary, NC).

Results: Results are presented in order for the 10, 15 and 20 mg/kg rifampin groups. There were 58, 57, and 53 patients evaluable for pharmacokinetics. Median (range) values for Cmax were 6.20 (0.62-12.55), 10.18 (0.58-27.00) and 13.33 (3.88-39.22), and for AUC0-6 24.94 (2.63-57.94), 43.13 (3.49-111.58) and 55.47 (13.63-132.88). Median ratios for the 15/10 and 20/10 mg/kg doses were Cmax 1.64 and 2.15; AUC0-6 1.73 and 2.22. Median Tmax was 2 hours across all groups, and median half-lives were 2.29, 2.46, and 2.31 hours. There were no statistically significant differences among the recorded adverse events across the 3 dosing groups.

Conclusions: Rifampin doses up to 20 mg per kg were well tolerated and produced slightly more than proportional increases in Cmax and AUC0-6. Peak concentrations, including in the 10 mg/kg/day arm, were higher and achieved more consistently at 2 hours than previously reported among TB patients in Peru treated with locally sourced rifampin. The concentrations in the control group in HIRIF were similar to those achieved in a recent dose-ranging study of rifampin in South Africa; Cmax in the 20 mg/kg arm in Peru was lower and more variable than that reported in the South Africa study (21.6 [16.0-31.9]). The present results, and those of other studies, support continued investigation of higher doses of rifampin for potential efficacy improvements and treatment shortening benefits.

Conflict of interest financial relationship(s): US National Institute of Allergy and Infectious Diseases U01AI091429
Abstract: P_19

Drug-Drug and Drug-Disease state interactions

Moxifloxacin is a potent in vitro inhibitor of OCT- and MATE-mediated transport of metformin and ethambutol

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Background: Diabetes mellitus (DM) impacts tuberculosis (TB) with increasing magnitude. At the moment, an estimated 15% of TB cases can be attributed to DM, which is expected to increase in the near future. It is largely unknown if simultaneous administration of tuberculosis (TB) drugs and the first choice antidiabetic metformin leads to drug-drug interactions (DDIs). Disposition of metformin is determined by organic cation transporters (OCTs) and multidrug and toxin extrusion proteins (MATEs), and therefore, any DDIs would primarily be mediated via these transporters. This study aimed to assess the in vitro inhibitory effects of TB drugs (rifampicin, isoniazid, pyrazinamide, ethambutol, amikacin, moxifloxacin and linezolid) on metformin transport. Furthermore, we investigated whether TB drugs are also substrates of OCTs and MATEs, and thus can become a victim of transporter-mediated DDIs.

Methods: HEK293 cells overexpressing OCT1, OCT2, OCT3, MATE1 and MATE2K were used to study TB drug-mediated inhibition of [14C]metformin uptake, and to test if TB drugs are transporter substrates. Metformin uptake was determined by quantifying [14C]metformin radioactivity and TB drug uptake was analyzed using LC-MS/MS. Curve fitting of concentration-dependent inhibition of transport and estimation of IC50 values were established by nonlinear regression analysis using GraphPad Prism software version 5.03 (GraphPad Software Inc., San Diego, CA, USA). DDI indices, or ratios, were calculated by dividing the maximal inhibitor concentration in plasma (e.g. Cmax of moxifloxacin was set at 6.0 mg/L (15 µM) and protein binding at 50%) by the transporter-specific in vitro IC50 value. Based on literature, a cut-off of ≥0.1 was assumed to warrant further prospective in vivo investigation. To estimate the substrate concentration at which half of the maximum transport velocity is obtained (Km), concentration-dependent uptake data were fitted to the Michaelis-Menten equation using GraphPad Prism.

Results: Moxifloxacin was the only TB drug identified as a potent inhibitor (DDI-index >0.1) of MATE1- and MATE2K-mediated metformin transport (IC50 of 12 µM (95% CI 5.1-29 µM) and 7.6 µM (95% CI 0.2-242 µM), respectively). Of all TB drugs, only ethambutol appeared to be a substrate of OCTs and MATEs. The affinity of ethambutol, as quantified by Km, amounted to 686 µM (95% CI 0-1521 µM) for OCT1, 314 µM (95% CI 0-646 µM) for OCT2, 1356 µM (95% CI 0-3584 µM) for OCT3, 2164 µM (95% CI 0-4838 µM) for MATE1 and 819 µM (95% CI 0-2660 µM) for MATE2K. MATE1-mediated ethambutol uptake was inhibited strongly (DDI-index >0.1) by moxifloxacin (IC50 14 µM (95% CI 3.4-43 µM)).

Conclusions: We found moxifloxacin to be a potent inhibitor of MATE1- and MATE2K-mediated metformin transport, identified ethambutol as a substrate of OCT1, OCT2, OCT3, MATE1 and MATE2K, and demonstrated that MATE1-mediated ethambutol uptake was inhibited by moxifloxacin. According to international DDI guidelines, our results warrant further in vivo interaction studies. The data could also serve as valuable input for physiologically-based pharmacokinetic (PBPK) modeling to predict intracellular and plasma drug concentrations of metformin and ethambutol and simulate clinical DDIs with these drugs. More emphasis should be placed on TB drug interactions mediated through transporters.

No conflict of interest
Abstract: P_20

Population PK/PD modeling

Pharmacokinetic Modeling and Limited Sampling Strategies based on healthy volunteers for Monitoring of Ertapenem in MDR-TB patients

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Background: Ertapenem is a widely used broad-spectrum antibiotic that can be administered once daily. Ertapenem is one of the newer carbapenems that is explored against Mycobacterium tuberculosis. Carbapenems in combination with clavulanic acid has attracted interest since activity was shown in a murine model of TB. Carbapenems appear to inactivate peptidoglycan cross-linking in M. tuberculosis. In the few MDR-TB patients that have been treated with ertapenem as part of a multidrug regimen; the drug appeared well tolerated during prolonged treatment. The free 40% of the time above the minimal inhibitory concentration (f40%T>MIC) was shown to be the most important pharmacokinetic/pharmacodynamics (PK/PD) parameter for ertapenem. To be able to calculate the f40%T>MIC, a good indication of the plasma concentration profile is mandatory. To assess 40%T>MIC in MDR-TB patients, we developed a limited sampling strategy using a population pharmacokinetic model based on healthy volunteers.

Materials and Methods: A population two-compartment model was based on data from 48 healthy volunteers using a two-stage Bayesian procedure. Bland-Altman analysis was performed to evaluate the correlation between the area under the plasma concentration-time curve from 0-24h (AUC0-24h) calculated and the AUC0-24h estimated with the pharmacokinetic model. Plasma concentrations of 12 patients with MDR-TB were fitted into the model. A Monte Carlo simulation (n=1000) was used to calculate limited sampling strategies. Additionally, the f40%T>MIC for MDR-TB patients was estimated with the population pharmacokinetic model. Bootstrap analysis was performed to determine the accuracy of the model and Passing and Bablok regression was performed to determine the agreement between the AUC0-24h calculated and the AUC0-24h estimated with the pharmacokinetic model.

Results: The pharmacokinetic parameters determined with bootstrap analysis were CLm 1.06 L/h, V1 0.08 L, fr 0.13, V2 0.05 L and CL12 2.56 L/h. This pharmacokinetic model has shown to estimate the AUC0-24h in MDR-TB patients with an overestimation of 6.8 (range: -17.2 – 30.7)%. The agreement between observed and model calculated AUC0-24h was best at a lower AUC0-24h. The best performing limited sampling strategy was found to be sampling at 1 and 5h (R² = 0.78, mean predictive error = -0.33% and a %root mean square error = 5.5). Drug exposure was overestimated by 4.2 (-15.2 – 23.6)%.

Conclusions: A pharmacokinetic model and limited sampling strategy, developed using data from healthy volunteers, showed to be adequate to predict drug exposure in MDR-TB patients.

No conflict of interest
Abstract: P_21

Drug-Drug and Drug-Disease state interactions

Isoniazid Clearance is Impaired among HIV/Tuberculosis Patients with High Levels of Immune Activation

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Introduction: Patients infected with HIV have chronic immune activation and cytokine dysregulation, characterized by increased CD38 and HLA-DR expression on CD8+ T cells (CD38+DR+CD8+). Immune activation and pro-inflammatory cytokines are known to regulate the expression and activity of some phase I xenobiotic metabolic enzymes and drug transporters. Patients with high levels of inflammation and immune activation due to other causes, such as bacterial sepsis or acute viral infections, demonstrate impaired drug metabolizing capacity.

Material & Methods: We conducted a prospective study of isoniazid pharmacokinetics and systemic immune activation prior to and one month after antiretroviral therapy (ART) initiation to test the hypothesis that elevated levels of systemic immune activation among adults with HIV/TB initiating ART would be associated with impaired clearance of isoniazid. The study procedures consisted of two study visits, with each visit conducted at the Infectious Disease Care Clinic at Princess Marina Hospital in Gaborone, Botswana. The first study visit occurred between 5 and 28 days after the initiation of anti-TB therapy, corresponding to steady-state conditions. All participants were eligible to return for a second pharmacokinetic visit during the intermittent phase of anti-TB therapy, provided that ART had also been initiated. We performed non-linear mixed effects modeling to measure the covariate effect of immune activation on isoniazid clearance in a model that also included N-acetyltransferase-2 (NAT-2) genotype and inter-occasional variability on clearance.

Results: We enrolled 40 patients in the pharmacokinetic visit prior to ART, and 24 patients returned for the second visit a median of 33 days after initiating ART. At the time of the first study visit, the median duration of anti-TB therapy was 20 days (range 7-65 days), and no patients were receiving ART. At the time of the second visit, the median duration of anti-TB therapy was 74 days (range 33 to 118 days), and participants had been receiving ART for a median of 33 days (range 5 to 44 days). Among the 38 participants with non-ambiguous NAT-2 genotype, 7 (18%) were classified as slow acetylators, 18 (45%) were intermediate acetylators, and 13 (33%) were rapid acetylators. The isoniazid concentration data were best described by a 2-compartment model with first-order elimination. After accounting for NAT-2 genotype, increasing levels of CD38+DR+CD8+ were associated with decreasing isoniazid clearance. There were no episodes of clinical hepatotoxicity among the study subjects during the observation period

Conclusions: We present the novel finding of decreasing isoniazid clearance among HIV/TB patients with increasing levels of immune activation. Future efforts should characterize the time course of this relationship, define the specific mediators of the effect, and explore the potential relationship between isoniazid accumulation, immune response, and the risk of hepatotoxicity.

No conflict of interest
Abstract: P_22

Drug-Drug and Drug-Disease state interactions

An interim analysis on the impact of diabetes mellitus on rifampicin population pharmacokinetics in Indian adult patients

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Introduction: Rifampin is the key sterilizing drug in the first-line tuberculosis (TB) treatment regimen. It has been suggested that TB patients with diabetes mellitus (DM) have lower plasma concentrations of rifampin, but findings have been variable between studies1,2. Therefore, a currently ongoing TB-DM clinical trial aims to investigate if, and to what extent DM affects rifampicin pharmacokinetics (PK) in Indian adult patients. Here, we present here an interim analysis of the first 92 patients of 675 expected in total.

Material & Methods: TB patients without DM (N=67) with a median body weight of 45 kg (minimum - maximum, 27-63 kg) or with DM (N=25) with a median body weight of 50 kg (35-74 kg) received thrice weekly rifampicin treatment for 6 months. Between week 4-6 and 10-12 of treatment, respectively, 4 blood samples were collected: pre-dose and at 0.5, 2 and 6 hours after rifampicin dose. A total of 487 PK observations after dose were available for analysis, of which 33% were below limit of quantification (BQL). Population pharmacokinetics were modeled using NONMEM 7.3 in which BQL samples were handled using the M3 method3. The influence of baseline body weight, drug formulation and diabetes mellitus were evaluated for each PK parameter. Parameter uncertainty was estimated using 200 bootstrap runs.

Results: A one-compartment PK model with a three-compartment transit model for oral absorption best described the data. Apparent clearance, CL/F, for the first occasion was estimated to be 7.8 L/h (relative standard error of 7%), volume of distribution, V/F, 69 L (13%) and mean oral transit time was 3.2 hours (5%). Inter-individual variability was included for CL/F and V/F and inter-occasion variability for transit compartment rate, Ktr. The influence of weight on CL/F and V/F were described by allometric scaling with fixed exponents 0.75 and 1, respectively. In addition, it was found that relative oral bioavailability was 37% (23%) lower for the second PK visit (week 10-12, p<0.001). This is most likely due to a change in rifampicin formulation from a 4 drug fixed dose combination to a 2 drug fixed dose combination. After inclusion of these covariates, no influence of diabetes on any of the PK parameters could be detected (p>0.05).

Conclusions: This interim analysis of an ongoing TB-DM clinical trial in Indian adult patients does not show any significant influence of diabetes on the pharmacokinetics of rifampicin. However, the population PK analysis of the full trial should be awaited to confirm these preliminary results.

References:
2. Ruslami, R. et al. Pharmacokinetics of Antituberculosis Drugs in Pulmonary Tuberculosis Patients with Type 2 Diabetes. 54, 1068–1074 (2010).

No conflict of interest
Abstract: P_23

Pharmacokinetics and Pharmacodynamics of Approved Drugs

Population pharmacokinetics of 1st-line antituberculosis drugs administered under three treatment strategies in TB/HIV patients from West Africa.

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Background: The Rafa study was designed to evaluate 3 TB treatment strategies in ARV-naïve TB/HIV patients: (1) standard tuberculosis treatment with efavirenz-based ART initiation after 2 months, (2) 50% higher dose of rifampicin, and (3) initiation of ART after two weeks. An improvement in TB outcome was observed in the high-dose rifampicin arm, but only amongst patients with <100 CD4+ count. The objective of this PK sub-study was to describe pharmacokinetics of rifampicin, isoniazid, pyrazinamide, and ethambutol (RHZE), evaluating differences in exposure between the treatment arms and addressing whether they could explain the observed difference in outcome.

Methods: Patients received weight-adjusted daily doses of a fixed-dose combination (FDC) containing RHZE. Blood samples were collected from 222 patients just before, and 2, 3, 6, and 10 hours post dose, at 4 to 8 weeks after starting tuberculosis treatment. Plasma concentrations of RHZE, deacetyl-rifampicin, and acetyl-isoniazid were quantified using LC-MS. Population pharmacokinetics was used to interpret the data and identity predictors of exposure, including the effect of treatment arm and CD4+ cell count.

Results: Rifampicin pharmacokinetics was described using a one-compartment model with liver first-pass effect. On average, exposure in the higher rifampicin dose arm was 71% higher compared to other treatment arms. A two-compartment disposition model with liver first-pass effect described the pharmacokinetics of isoniazid, separating acetylation, which leads to the formation of acetyl-isoniazid, from other routes of elimination. A mixture model was used to classify metabolic status of patients, distinguishing between fast and slow acetylators with approximately equal proportions. Patients in the early ART arm had 34% increased acetylation clearance. Pyrazinamide and ethambutol pharmacokinetics were described using one-compartment and two-compartment models, respectively. A very large variability in exposure was observed for rifampicin and isoniazid. Of note, 60% lower exposures of both rifampicin and isoniazid were detected in patients treated with two of the drug batches used in the study. Pyrazinamide and ethambutol exposures were reduced by ~15% in the same patients. Allometric scaling of all clearance and volume parameters for the four drugs was best characterised using fat-free mass, as opposed to total body weight. There were no differences in exposure when comparing patients with CD4 count above or below 100 cells/mm3.

Conclusions: High-dose rifampicin led to a more-than-proportional increase in exposure. Efavirenz-based ART reduces the exposure to isoniazid, and this effect is possibly more pronounced in fast metabolisers, who already experience lower isoniazid concentrations. Consistent with previous studies, our results suggest that fat-free mass may be more appropriate than total body weight to design dosing strategies. The difference in outcome observed in the high-dose rifampicin arm between patients below and above 100 CD4+ cell count does not seem to be driven by differences in PK exposure.

No conflict of interest
Abstract: P_24

Population PK/PD modeling

**Genetic determinants of the pharmacokinetic variability to rifampicin in Malawian adults with pulmonary tuberculosis**

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**Background:** Variable exposure to anti-tuberculosis (TB) drugs may be associated with poor clinical outcomes. Patient physiology, co-morbidities, concomitant medications and dietary intake all influence drug exposure. However, patient genotypes for drug metabolising enzymes and transporters may explain up to 30% of PK variability for all drugs12-14. Although Africans have the highest degree of genetic diversity worldwide15 and sub-Saharan Africa accounts for a large proportion of global TB incidence and mortality, data on the pharmacogenetic determinants of rifampicin exposure amongst TB-endemic African populations are sparse.

In this study we assessed the impact of SNPs in SLCO1B1 and AADAC on plasma exposure to rifampicin amongst Malawian adults with smear-positive pulmonary TB.

**Methods:** A population analysis was performed with 358 plasma drug concentrations from 174 adults with pulmonary TB receiving a rifampicin containing regimen for at least 4 weeks. DNA was available from all patients and was used to genotype two rifampicin transporting or metabolising genes: SLCO1B1 (rs11045819, rs4149032) and AADAC (rs1803155, rs61733693) by real-time PCR allelic discrimination. Combining genetic and demographic covariates, non-linear mixed effects modelling (NONMEM v.7.2), was used to estimate pharmacokinetic parameters, inter-individual variability, residual error, and the influence of different patient characteristics. The model was validated by means of simulation and visual predictive check.

**Results:**

A one-compartment model with a transit compartment to describe drug absorption best described the data. Population clearance was 19.5 l/h with inter-patient variability of 27.6%. An allometric scaling model for clearance and volume of distribution as a function of weight was applied. The only statistically significant covariate (on clearance) was sex.

**Conclusions:** Wide-ranging variability in plasma exposure to rifampicin amongst Malawian adults with pulmonary TB cannot be explained by genetic heterogeneity in SLCO1B1, as suggested from other African populations. The true significance of pharmacogenetic influences on TB drug disposition can only be established through consistent observation across diverse and adequately powered cohorts.

No conflict of interest
Abstract: P_25
Pharmacokinetics and Pharmacodynamics of Approved Drugs

Low rifampicin and isoniazid concentrations are associated with delayed sputum conversion in HIV positive patients co-infected with tuberculosis in Uganda.

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Background: HIV-positive patients co-infected with tuberculosis (TB) have anti-TB drug concentrations lower than reference ranges; however the relationship between concentrations of anti-TB drugs and treatment response remains controversial. We sought to evaluate if there is an association between low concentrations of first-line anti-TB drugs and delayed sputum conversion in a cohort of HIV-TB co-infected Ugandan adults.

Methods: We enrolled HIV-infected Ugandan adults diagnosed with first episode of pulmonary TB. Patients underwent pharmacokinetic sampling 1, 2, and 4 hours after drug intake to estimate the maximum drug concentrations (eCmax); at 2, 8, and 24 weeks of TB-treatment using high-performance liquid chromatography. Low concentrations were defined as an eCmax below the previously described cut-offs: rifampicin <8mg/L and isoniazid <3mg/L. Sputum conversion was defined as conversion of sputum culture or smear from positive to persistently negative results during follow-up. Cox regression and Kaplan-Meier curves were used to determine the association between sputum conversion dynamics and anti-TB drug concentrations.

Results: From April 2013 to May 2015, we included 226 HIV infected patients with positive sputum cultures or smears at baseline; 58% were male. Patients with low isoniazid and rifampicin concentrations at any time point were less likely to undergo sputum conversion before the end of follow-up compared to those with normal concentrations at all time-points (HR:0.51; 95%CI:0.35-0.72; P<0.001 and HR:0.61; 95%CI:0.44-0.84; P=.003 respectively). In addition, patients with ≥1 drugs below the cut-off had a higher probability of remaining culture/smear positive over time compared to those with no drug below the cut-off.

Conclusion: Low isoniazid or rifampicin concentrations in HIV-TB co-infected patients resulted in delayed sputum conversion. This has potential implications on TB transmission.

No conflict of interest
Abstract: P_26

TB Treatment in Special Populations

Attainment of Target Rifampin Concentrations in Cerebrospinal Fluid during Treatment of Tuberculous Meningitis: A Pharmacokinetic Modeling and Simulation Study

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Introduction: There is considerable uncertainty regarding the optimal dosing regimen for the treatment of tuberculosis (TB) meningitis with the first-line anti-TB drugs. Rifampin auto-induces its own metabolism, reaching steady-state conditions after approximately 2 months of daily treatment. We sought to determine the impact of auto-induction on the CSF concentrations of rifampin during the intensive phase of TB meningitis treatment.

Materials & Methods: We evaluated a pharmacokinetic model of rifampin CSF concentrations during TB meningitis treatment with additional individual-level CSF concentration data not included in model development. To this model we added a mechanistic enzyme turnover compartment to incorporate auto-induction of systemic clearance. We then performed a Monte Carlo simulation of rifampin CSF concentrations in TB meningitis patients (n=10,000) under intensive rifampin dosing strategies that had been examined in recent clinical trials, along with the World Health Organization (WHO) dosing algorithm. Minimum inhibitory concentrations (MICs) for rifampin were sampled from a previously reported wild-type distribution. For each rifampin dosing strategy, we examined the AUC0-24/MIC ratio achieved on the 3rd day of treatment (pre-induction) and the 28th day of treatment (post-induction). To determine the probability of target attainment for each dosing strategy, we compared these AUC0-24/MIC ratios with the target ratio of 30, which was associated with a 1-log10 decline in colony-forming-units of extracellular M. tuberculosis.

Results: We included an upper (0.13) and lower (0.08) bounds for the partition coefficient of rifampin from plasma into CSF as a sensitivity analysis. Across all simulated patients on the 3rd day of treatment, 46-66% attained the target AUC0-24/MIC ratio under the standard WHO dosing scheme, 66-85% attained the target under the high-dose oral dosing scheme, and 81-93% attained the target with 750 mg intravenous once-daily dosing (corresponding to a mean of 13.6 mg/kg in the simulated population). By the 28th day of treatment, the target attainment probabilities for each of these dosing strategies decreased to 29-45%, 46-66%, and 63-83%, respectively.

Conclusions: In this simulation of rifampin CSF concentrations during the intensive phase of treatment, we found that attainment of the target rifampin AUC0-24/MIC ratio in CSF decreases as a consequence of auto-induction of systemic clearance. Few patients would be expected to attain the pharmacodynamic target in CSF when the rifampin MIC is 0.5 mg/L or greater, even with the intravenous dosing strategy. Future clinical trials of intensive rifampin dosing strategies for the treatment of TB meningitis should account for the auto-induction of systemic clearance.

No conflict of interest
Abstract: P_27

Drug Development and optimization: Approaches & Tools

Cost-utility Analysis of Treating Tuberculosis Patients with Intermediate Susceptibility with a Higher Rifampicin and Isoniazid Dose

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Background: In addition to ‘drug-susceptible’ and ‘multi-drug resistant’ categories within TB, we propose to implement an intermediate susceptibility category. This intermediate category are the minimal inhibitory concentrations between the currently used susceptibility breakpoint and a lower susceptibility breakpoint that was suggested based on new data. To determine whether a patient is intermediate susceptible, a second susceptibility test is performed for patients who are thought to be drug-susceptible. We suggest to treat the intermediate susceptible patients with high-dose isoniazid and rifampicin three times a week for 12 weeks to prevent treatment failure and to minimize the relapse rate. This study investigates cost-utility of this more tailored treatment strategy.

Materials and Methods: A Markov model was used to evaluate costs and Quality Adjusted Life Years (QALYs) associated with doing either one drug susceptibility test (current care) or two drug susceptibility tests, the latter to determine if the Mycobacterium tuberculosis strain is intermediate susceptible, and treating patients accordingly. The analysis was performed from a societal perspective, for both a high income (the Netherlands) and a low income (Belarus) country. Patients have a certain risk for a positive (treatment completed) or a negative outcome (treatment failure or death) as well as relapse within 5 years after an initially positive treatment outcome. One way sensitivity analyses were performed to determine the uncertainty surrounding the results. Additionally a cost-effectiveness acceptability curve (CEAC) was made to summarize the uncertainty in estimates of the analysis. Since there is limited data on the outcomes of high-dose isoniazid and rifampicin treatment, scenario analysis were also performed.

Results: Results show that for Belarus, the introduction of the intermediate susceptibility and subsequent treatment with high-dose isoniazid and rifampicin saves costs and increases QALYs. However, since in the Netherlands the success rate of normal-dose first-line treatment is among the highest in Europe, and even higher than the average success rate for first-line high-dose treatment used in the model, introducing the intermediate susceptibility seemed less advantageous for the Dutch situation. Therefore, we performed a scenario analysis assuming an elevated success rate for high-dose first-line treatment in the Netherlands, which led to the same results as for Belarus, i.e. gaining QALYs and saving costs. In Belarus (lower-income country) the results were more robust since in this country multidrug-resistant tuberculosis is more common. Results were sensitive to assumptions on, amongst others, therapeutic failure with high-dose first-line anti-TB treatment, acquired drug-resistance after high-dose first-line anti-TB drugs, relapse rate and the costs associated with terminal care.

Conclusion: Introduction of high dose for the intermediate susceptible category seems promising and efficient, and could also reduce drug-resistance in the long term.

No conflict of interest
Abstract: P_28

Pharmacokinetics and Pharmacodynamics of Approved Drugs

Macrophage Intracellular Kill Rate is Predictive of Tuberculosis Treatment Duration

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Tuberculosis (TB) treatment is long and complex, typically involving a combination of drugs taken for 6 months. Improved drug regimens to shorten and simplify treatment are urgently required, however a major challenge to TB drug development is the lack of predictive pre-clinical tools. To address this deficiency, we have adopted a new high-content imaging-based approach capable of defining the killing kinetics of first line anti-TB drugs against intracellular Mycobacterium tuberculosis (Mtb) residing inside macrophages.

Through use of this pharmacokinetic-pharmacodynamic (PK-PD) approach we demonstrate that the killing dynamics of the intracellular Mtb sub-population largely defines clinical TB treatment duration. Integrated modelling of intracellular Mtb killing alongside conventional extracellular Mtb killing data, generates the biphasic responses typical of those described clinically.

Our model supports the hypothesis that the use of higher doses of rifampicin (35 mg/kg) will significantly reduce treatment duration.

Our described PK-PD approach offers a much needed decision making tool for the identification and prioritisation of new therapies to reduced TB treatment duration.

No conflict of interest
Abstract: P_29

Drug-Drug and Drug-Disease state interactions

Assessment of Pharmacodynamic Interactions in the Mouse using the Multistate Tuberculosis Pharmacometric Model and the General Pharmacodynamic Interaction Model

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Background: The aim of this work was to investigate pharmacodynamic (PD) interactions in Mycobacterium Tuberculosis infected mice using the Multistate Tuberculosis Pharmacometric (MTP) and the General Pharmacodynamic Interaction (GPDI) models.

Methods: Rifampicin, isoniazid, ethambutol or Pyrazinamide were given for 4 weeks in monotherapy. Colony forming unit (cfu) was measured after 1, 2 and 4 weeks treatment (9 mice/occasion). Fixed doses of each drug were used in different combinations and cfu was measured up to 24 weeks treatment (3 mice/occasion). Natural growth data was collected up to 21 days after infection. Population pharmacokinetic models for each drug were developed.

Results: Rifampicin alone killed fast-multiplying (F), slow-multiplying (S) and non-multiplying (N) bacteria and inhibited the growth of F. Isoniazid alone killed F and S but together with pyrazinamide, isoniazid also killed N. When combing rifampicin and isoniazid, an effect against S and N less than expected additivity was quantified (antagonism; increased log10 cfu/mL by 0.79 and 0.86, respectively). Ethambutol and rifampicin in all four-drug combination showed synergism against N, decreasing log10 cfu/mL by 2.84.

Conclusion: The results suggest that the MTP and the GPDI models can be combined in order to allow for model-based assessment of tuberculosis PD interactions in mice.

No conflict of interest
Abstract: P_30

Population PK/PD modeling

Pre-clinical Model Informed Susceptibility Characterization and Pharmacodynamic Interaction Assessment in Early Tuberculosis Drug Development

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Introduction: As known, tuberculosis is a disease requiring a combination of drugs to effectively defeat the bacterial infection. From many perspectives establishing an initial optimal combination of drug dosages is not reasonable to carry out in a clinical setting. This information could rather be provided from a pre-clinical setting. This work aimed at developing a preclinical in vitro model informed approach to the selection of drug combinations in early tuberculosis drug development. The approach was evaluated using combination exposures of rifampicin (RIF), isoniazid (INH) and ethambutol (EMB).

Material and Methods: In vitro time kill experiments were performed with Mycobacterium tuberculosis (M. tuberculosis) genotype strain Beijing 1585 using both single and combination series of RIF, INH and EMB concentrations. Viability, defined as colony forming units (cfu), was assessed at day 1, 2, 3 and 6 after drug exposure. The Multistate Tuberculosis Pharmacometric (MTP) model framework was used to characterize the natural growth and effect of drug exposure on the bacteria. Pharmacodynamic interactions between the three drugs during combination exposure was quantified on effect parameter level with the General Pharmacodynamic Interaction (GPDI) model.

Results: The characterization of drug effect from mono exposure and combination(s) of RIF, INH and EMB revealed that RIF exerted effect on fast-, slow- and non-growing bacteria whilst INH and EMB were found to exert kill effect on only the fast- and slow multiplying bacterial state. Quantification of pharmacodynamic interactions for combinations of the three drugs on the kill effect on the fast multiplying state bacteria showed that in combination RIF decreased INH EC50 (identified in mono exposure) by 68 % and EMB EC50 (identified in mono exposure) by 99%. Isoniazid however showed no deviation from an additive effect on the EC50 (identified in mono exposure) of RIF and EMB. Ethambutol was found to lower RIF EC50 (identified in mono exposure) by 66% but showed no deviation from an additive interaction on the EC50 (identified in mono exposure) of INH. For the kill of slow multiplying state bacteria all pharmacodynamic interactions was found to lead to increases in the EC50’s identified in mono exposure for the three drugs.

Conclusions: We have in this study developed a preclinical model informed approach for characterization of susceptibility and identification of pharmacodynamic interactions in early tuberculosis drug development. The combination of pharmacometric models and preclinical information constitutes a powerful approach enabling characterization of both bacterial properties and drug effect at level that is beyond what is possible using information from a clinical setting. The interaction assessment utilized in this study is highly suitable as input to selection of phase 2b anti-tuberculosis combination regimens as it allows for distinction of drug A’s interaction with drug B and vice versa.

No conflict of interest
Abstract: P_31

Drug Development and optimization: Approaches & Tools

Collaborative approaches to defining contribution of animal models to prediction of clinical efficacy of TB therapies

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Introduction: Mouse model data has played a central role in preclinical development of anti-tuberculosis drugs despite ongoing debate about representativeness and reproducibility. Within the PreDiCT-TB consortium, close collaboration between experimentalists and statistical modellers has been central to optimising designs and applying a common modelling approach to analysis of mouse experiments performed for a common set of drug combinations. Collaborating with external scientific partners, PreDiCT-TB has begun to assemble a more comprehensive database of mouse studies than previously, facilitating comparisons between such models and also with clinical outcomes on the basis of ranking of treatments and their effect sizes. This meta-analytic approach has been informative in other therapeutic areas and promises to lead to a deeper understanding of the strengths and weaknesses of this key step in preclinical development.

Material & Methods: Timecourse profile datasets of M.Tb load in mice under therapy, typically CFU plated on solid media from lung homogenate, were fitted with mathematical models describing bacterial elimination by nonlinear regression methods. Empirical models describing a monoexponential elimination of M. Tb were generally applied and exponential elimination rate constants (k_net) estimated – this parameter is equivalent to the slope of elimination seen with log-transformed CFU data. The relative efficacy of therapies was assessed by ranking them in order of their values for this parameter – faster elimination rates reflected in a more negative k_net parameter value.

Results: Ranking tables, according to k_net for various therapies in 3 mouse models are presented with correlation coefficients to compare parameter values and rankings in the separate models against each other, and a meta-analysis with accompanying Forrest plot was carried out to derive a general ranking of therapies in mice. Finally all mouse rankings were compared to rankings of therapies in a clinical setting, based on several endpoint measures of efficacy (e.g. EBA 0-x, TTP at 8 weeks etc.) derived by a separate meta-analysis also carried out under Predict-TB.

Conclusions: Of the models analysed so far the Janssen mouse dataset showed the closest match to the ranking of therapies in human, with a general combined mouse model ranking showing some correlation with clinical rankings of EBA0-2 and 8 week TTP data. Ongoing work will analyse and incorporate further data from other mouse models.

No conflict of interest
Abstract: P_32

Pharmacokinetics and Pharmacodynamics of Approved Drugs

Potentiating the efficacy of moxifloxacin and linezolid in the treatment of multidrug resistant tuberculosis by efflux pump inhibition and cell membrane destabilization

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Background: The current treatment of tuberculosis (TB) is complicated by the emergence of multi-drug resistant TB (MDR-TB). As a result, there is an urgent need for new powerful TB regimens and novel strategies. In this study we aim to potentiate a moxifloxacin – linezolid backbone as treatment for MRD-TB with efflux pump inhibitors verapamil and timcodar as well as with drugs that act on the mycobacterial cell wall stability like colistin and SQ109.

Materials & Methods: Using a time kill kinetics assay the activity of moxifloxacin, linezolid, verapamil, timcodar, colistin and SQ109 as single drugs against Mycobacterium tuberculosis was evaluated. In addition the activity of the moxifloxacin + linezolid backbone in combination with one of the potentiator drugs was assessed.

Results: As little as 0.125 mg/L moxifloxacin achieved 99% killing of Mycobacterium tuberculosis after six days of exposure. Linezolid showed moderate killing but 99% killing was not achieved. Verapamil, timcodar and colistin only resulted in killing with the highest concentrations tested (64 – 256 mg/L) but 99% killing was not achieved. SQ109 resulted in complete elimination after one day of exposure to 256 mg/L and in 99% elimination after six days of exposure to 1 mg/L SQ109. Furthermore, we found that colistin added to the backbone resulted in increased elimination. Verapamil, timcodar and SQ109 showed no added value to the moxifloxacin + linezolid backbone.

Conclusions: We conclude that colistin potentiates the activity of the moxifloxacin + linezolid backbone against Mycobacterium tuberculosis, this suggests its potential role in further studies on the applicability of a moxifloxacin + linezolid treatment of MDR-TB.

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TB Treatment in Special Populations

First pharmacokinetic study using dried blood spot sampling of antituberculosis drugs in Paraguayan children.


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Introduction: Dried blood spot sampling (DBS) for the purpose of pharmacokinetic (PK) studies and Therapeutic Drug Monitoring (TDM) has unique advantages over conventional concentration measurements, including decreased patient burden, sample stability upon storage and decreased transporting costs. Therefore DBS may overcome practical problems of TDM in tuberculosis (TB) treatment in remote areas.

Materials & Methods: This was a DBS clinical validation and descriptive PK study among children with TB in Paraguay who were treated according to the revised WHO dosing scheme for children, using adult fixed-dose combination tablets (H75, R150, Z400, E275) in the absence of paediatric formulations. Sampling was performed prior to observed drug intake (t=0) and at t=2, 4 and 8h and consisted of a DBS sample and a conventional venous sample. All samples were analysed by means of validated LC-MS/MS methods. DBS is not suitable to measure isoniazid due to analytical recovery issues. Passing-Bablock regression and Bland-Altman plots were used to assess agreement between DBS and plasma concentrations. Predictive performance was quantified with median percentage prediction error (MPPE) and median absolute percentage prediction error (MAPE) as measures for accuracy and precision, respectively. PK analyses were performed using non-compartmental methods. The percent of patients attaining (adult) population PK values for Cmax (R 8-12; H 3-6; Z 20-50 and E 2-6 mg/L) and for AUC0-24h (R 41.1; H 15.2; Z 380; E 23.5 mg*h/L; Magis et al, Int J Antimicrob Agents. 2014;44:229-34) was computed.

Results: Fourteen patients completed PK sampling; 36% was female, their median age was 1.5 years (range 0.5-15) and median weight was 11 kg (range 6-53). Median dose was 14 mg/kg (range 8-27) for rifampicin, 7 mg/kg (range 4-13) for isoniazid, 38 mg/kg for pyrazinamide (range 22-72) and 26 mg/kg (range 15-49) for ethambutol. Passing-Bablock regression showed no significant proportional or systematic bias for each of the TB drugs. Use of a conversion factor (ratio DBS:plasma) resulted in good predictive performance for rifampicin and pyrazinamide (MPPE and MAPE <15%). Ethambutol DBS showed low precision with MAPE 45%. PK parameters (geometric means) based on DBS sampling (or plasma sampling; isoniazid, ethambutol) were: rifampicin Cmax 5.5 mg/L, AUC0-24h 25 mg*h/L, Thalf 1.7 h, CL 7.1 L/h and Vd 18 L; isoniazid Cmax 3.4 mg/L, AUC0-24h 17 mg*h/L, Thalf 2.3 h, CL 6.3 L/h and Vd 22 L; pyrazinamide Cmax 44 mg/L, AUC0-24h 519 mg*h/L, Thalf 5.8 h, CL 1.7 L/h and Vd 14 L; and ethambutol Cmax 2.3 mg/L, AUC0-24h 16 mg*h/L, Thalf 4.5 h, CL 25 L/h and Vd 208 L. Target attainement for Cmax was 27% for rifampicin, 71% for isoniazid, 100% for pyrazinamide and 71% for ethambutol.

Conclusions: This is the first clinical validation study of a DBS sampling method in children with TB. This innovative sampling method was successfully used for PK parameter analysis for rifampicin and pyrazinamide, but not for ethambutol. Despite recommended higher doses still a minority of children (~30%) reached average targeted adult rifampicin exposures. New paediatric formulations should be made available and procurable worldwide as soon as possible.

No conflict of interest
Abstract: P_34

Drug Development and optimization: Approaches & Tools

Performance of an app measuring spot quality in dried blood spot sampling

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Introduction: The Dried Blood Spot sampling (DBS) method gives patients and health care workers the opportunity for remote sampling using a drop of blood from a fingerprick on a sampling card which can be send to the laboratory by mail. Laboratory analysts frequently reject DBS samples because of poor sampling performance, which delays adequate monitoring of a patients’ blood drug concentration. We developed a web-based application (Web-app) measuring the quality of DBS at the moment of sampling using a smartphone or computer. The patient takes a picture of the blood spot using a smartphone, uploads it into the Web-app and the Web-app determines the spot quality (sufficient or insufficient). When an insufficient spot is produced the Web-app asks the patient or health care worker to resample until a sufficient spot is produced. We hypothesize that the use of this app will reduce rejection rates of DBS samples in clinical practice. We aim to measure the performance of this Web-app before implementation of this app in clinical practice.

Materials & Methods: The Dried Blood Spot App is a responsive web-based App accessible in the browser on smartphone, tablet or desktop pc. The app uses HTML5, Javascript and CSS technology. The results of the app was compared to a golden standard consisting of the combined judgment of two analysts with extensive experience in DBS analysis. Based on rejection rates observed in clinical practice performance qualification was set at 95% accurate evaluation. A samples size of at least 186 spots was required for qualification of the app. Samples were collected by a trained phlebotomist using the same sampling method the patients use at home. These samples were photographed and analyzed using the Web-app.

Results: 221 samples were collected on 204 different cards from 181 different patients. The app showed a performance of 90.0% with 4.1% false positives and 5.9% false negatives. False negative results will lead to (unnecessary) patients resampling until a sufficient spot is created and therefore will not lead to delayed monitoring. False positives will lead to sending in insufficient quality spots by the patient leading to delayed monitoring.

Conclusion: Although performance of 95% was not met, the current version of the Web-app will lead to a rejection rate of 4.1% DBS samples and is feasible for clinical application. The app will be implemented in clinical practice in the near future.

Conflict of interest: financial relationship(s): App was financially supported by MSD

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