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Are external grants or funds being used to support this research?: No external grants or funds are being used to support this research.

How did you learn about the YODA Project?: Data Holder (Company)

Conflict of Interest

http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestorspandemicsignedjs.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestorspandemicsignedjwa.pdf
http://yoda.yale.edu/system/files/yoda_project_coi_form_for_data_requestorspandemicjeb_14-5-2018.pdf

Certification

Certification: All information is complete; I (PI) am responsible for the research; data will not be used to support litigious/commercial aims.

Data Use Agreement Training: As the Principal Investigator of this study, I certify that I have completed the YODA Project Data Use Agreement Training

Associated Trial(s):

1. [NCT00449644 - A Phase II, Placebo-controlled, Double-blind, Randomized Trial to Evaluate the Anti-bacterial Activity, Safety, and Tolerability of TMC207 in Subjects With Newly Diagnosed Sputum Smear-positive Pulmonary Infection With Multi-drug Resistant Tuberculosis](#)
2. [NCT00910871 - A Phase II, Open-label Trial With TMC207 as Part of a Multi-drug Resistant Tuberculosis Treatment Regimen](#)

[\(MDR-TB\) Treatment Regimen in Subjects With Sputum Smear-positive Pulmonary Infection With MDR-TB](#)

What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Pharmacokinetics in type 2 diabetes mellitus patients using bedaquiline for tuberculosis (PANDEMIC).

Narrative Summary:

Multidrug resistant tuberculosis (MDR-TB) is associated with worsening glycaemic control in type 2 diabetes mellitus (T2DM). (1) Vice versa, T2DM is a risk factor for MDR-TB. (2) While MDR-TB is increasing (3), incidence of T2DM is also rising. (4) Thus the number of MDR-TB cases related to T2DM is also expected to rise. It is well documented that T2DM patients have altered pharmacokinetics (PK) due to disease related changes in absorption, distribution and metabolism. (5) Yet, it is unknown whether this is the case for the new MDR-TB drug bedaquiline (BDQ). T2DM may affect BDQ exposure, resulting in reduced efficacy. In this study we will evaluate the PK of BDQ in T2DM patients.

Scientific Abstract:

Background: Whereas the safety and efficacy of BDQ has been proved in published randomized controlled trials (RCTs) in MDR-TB populations, less is published about the PK in patients with comorbid T2DM. It is well documented that T2DM patients have altered PK due to disease related changes in absorption, distribution and metabolic processes.(5) E.g. for chlorzoxazone Vd/F is increased by 250% in T2DM patients compared to healthy volunteers.(6) Also, CYP3A4 protein level and enzymatic activity is significantly decreased in T2DM patients, which may affect BDQ clearance.(7) As such, T2DM may thus affect BDQ exposure and, in turn, result in differences in efficacy. In this study we will evaluate, for the first time, the PK of BDQ in MDR-TB patients with comorbid T2DM. **Objective:** The objective of this study is to quantitate the effect of T2DM on the PK of BDQ in MDR-TB patients with comorbid T2DM using metformin with or without a sulfonylurea derivate (SUD), compared to MDR-TB patients without T2DM.

Study design: Retrospective case-control study.

Participants: MDR-TB patients with or without comorbid T2DM using metformin with or without a SUD.

Main Outcome Measure(s): Plasma concentrations of BDQ. Secondary endpoints are pharmacokinetic parameters (e.g. area under the BDQ plasma concentration time curve, C_{max}, time to reach C_{max}, trough concentration, half-life, clearance, volume of distribution and elimination rate constant).

Statistical Analysis: A population approach PK model will be developed, describing the individual plasma BDQ concentrations over time.

Brief Project Background and Statement of Project Significance:

TB is associated with worsening glycaemic control in T2DM.(1) Vice versa, T2DM is a risk factor for the development of TB (8) and is associated with poorer TB outcomes.(3,4) Moreover, T2DM is a risk factor for development for MDR-TB.(2) While resistance against first-line drugs is increasing,(3) the incidence of T2DM is also rising.(4) As such, the number of MDR-TB cases related to T2DM is expected to rise. Therefore, the WHO calls for action and highlights the need for an integrated approach to tackle the deadly linkage of these two diseases. (11)

MDR-TB, defined as TB that is resistant to at least isoniazid and rifampicin, has an estimated incidence of 480.000 patients and 190.000 people died as a result of it in 2014.(12) For MDR-TB, the WHO recommends a treatment period of up to 24 months with a combination of four or more second-line anti-TB drugs.(13) However, these older second-line drugs are less potent, cause more adverse drug events, demand a longer course of therapy with accompanying high treatment costs.(11,12) To increase treatment success for MDR-TB, the WHO supports the development of new drugs.(12)

One of these novel drugs is BDQ (Sirturo), which efficacy is dependent on its minimal inhibitory plasma

concentration (MIC).(16) BDQ is subject to hepatic clearance, particularly by CYP3A4 metabolism.(17) Polymorphism of CYP3A4 leads to changes in BDQ metabolism and thus BDQ exposure.(18) Variance of the CYP3A4*22 allele is found to have a 2.5-fold decreased activity. The frequency of this allele is around 3.2-10.6% in Caucasians, as a result ~1% of Caucasians are poor metabolizer (PM) and ~10% intermediated-metabolizers (IM).(19)

Whereas the safety and efficacy of BDQ has been proven in randomized clinical trials in MDR-TB populations, less is known about the pharmacokinetics (PK) and pharmacodynamics in patients with comorbid T2DM. It is well documented that T2DM patients have altered PK due to disease-related changes in absorption, distribution and metabolism processes.(5) Also, poor glycaemic control correlates with changes in PK.(20) Therefore we will investigate the effect of glucose control in T2DM patients on the PK of BDQ.

In newly diagnosed T2DM patients, lifestyle intervention is the first line of treatment. The first step of pharmacological intervention is administration of metformin. In case of insufficient glucose control a sulfonylurea is added. Next step in treatment is use of insulin.(21) In low- and middle-income countries, oral diabetes drugs (metformin and SUD's) are the most widely available. In these countries, insulin is more difficult to obtain, let alone the more recently available T2DM drugs (e.g. SGLT2 inhibitors). As such, we aim to include T2DM patients that are on stable use of metformin and sulfonylureas.(22)

Understanding the PK of BDQ in patients with T2DM can aid the development of tailored dosing regimens that will enhance both BDQ efficacy and safety. To our knowledge this is the first study that investigates the effect of T2DM on PK of BDQ.

Specific Aims of the Project:

The primary aim of this study is to quantitate the differences in BDQ pharmacokinetics in MDR-TB patients with- or without T2DM using population approach modeling and simulation techniques.

The secondary aim is to identify covariates that explain the variability in pharmacokinetic parameters between MDR-TB patients with and without comorbid T2DM, with specific focus on parameters that relate to BDQ PK of T2DM-status;

- Blood chemistry ([fasting-] plasma glucose, Hb1AC, creatinine, uric acid, hemoglobin, hematocrit, albumin, total protein)
- Vital signs (blood pressure)
- Urine chemistry (total protein, creatinine, sodium, potassium, urea, albumin [urinary albumin:creatinine ratio])
- metabolism status (CYP3A4)
- co-medication
- demographics (T2DM status, bodyweight, age, sex, race, dose)

We hypothesize that MDR-TB patients with comorbid T2DM have different BDQ exposure compared to MDR-TB patients without comorbid T2DM.

What is the purpose of the analysis being proposed? Please select all that apply.

New research question to examine treatment effectiveness on secondary endpoints and/or within subgroup populations

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:

Inclusion criteria:

MDR-TB patients without T2DM

- Body mass index (BMI) between 18.5 and 30 (kg/m²)
- HbA1c <42 mmol/mol and fasting plasma glucose < 6,1 mmol/L.

MDR-TB patients with comorbid T2DM:

- Diagnosed with T2DM by physician.
- Using metformin with or without a sulfonylurea, or solely a sulfonylurea.
- BMI between 18.5 and 40 (kg/m²)

Exclusion criteria:

- Any medication, surgical or medical condition which might significantly alter the absorption, distribution, metabolism, or excretion of study medication including, but not limited to any of the following:
- Major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, or bowel resection

- Gastro-intestinal ulcers and/or gastrointestinal or rectal bleeding within last six months
- Pancreatic injury or pancreatitis within the last six months
- Evidence of hepatic disease as determined by any one of the following: ALT or AST values exceeding 3x ULN at inclusion visit, a history of hepatic encephalopathy, a history of esophageal varices, or a history of portocaval shunt.
- Use of inducers and/or inhibitors of the cytochrome P-450 3A4 isoenzyme CYP3A4.

Main Outcome Measure and how it will be categorized/defined for your study:

Main outcome measure is the individual plasma concentrations of BDQ over time.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:

The main predictor is the predicted individual plasma concentration of BDQ over time, defined as the result of a population pharmacokinetic model.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:

Other variables of interest are covariates that explain the variability in pharmacokinetic parameters between MDR-TB patients with and without comorbid T2DM, with specific focus on parameters that relate to BDQ pharmacokinetics and/or T2DM-status, as specified in the secondary aims.

Relationships between covariates and pharmacokinetic parameters will be visually explored and relevant relationships (e.g. $r^2 > 0.50$) will be formally tested during the model development. Covariates which are clinically relevant and have the highest correlation with the empirical Bayes' estimates of the parameters, will be introduced in the model.

Continuous covariates will be included by centering at a reference value at the median of the observed covariate values. Power functions, exponentials, and linear functions may be explored for the covariate relationships. Covariate analysis is performed by forward inclusion followed by backward elimination. Covariate parameter estimates (including S.E.) and their back transformed values (including 95% CI) will be reported. Histograms will provide information on the distributions of the continuous covariates used in the population PK model, as will QQ-plots.

Statistical Analysis Plan:

The statistical analysis closely follows the guidelines of the United States Food and Drug Administration for performing and reporting population pharmacokinetic analyses and literature on best practices and guidance in population modelling.(25,26) To meet software specifications, data will be transformed. E.g. all variables will be merged on the basis of a unique subject identifier number and time point into a single dataset. The resulting dataset will contain, per data row, unique subject-specific information per time point.

Population PK-model

Pharmacometric analysis will be performed using nonlinear mixed effect modeling. Nonlinear mixed effect modeling considers the repeated observations as a function of time in a population of individuals. The structural model consists of a structural pharmacokinetic model, of which PK parameters are allowed to vary between individuals, and a residual error structure. The population parameter typical values (e.g. clearance and volume of distribution), spread between individuals (interindividual variability) and spread within individuals (intraindividual variability) are estimated by minimizing the difference between model predictions and the observations: NONMEM reports an objective function value (OFV) which is the -2 times log likelihood.

Different model structures will be explored for most appropriate description of the interindividual variability and intraindividual variability. Using the population values (both location and spread), individual specific empirical Bayes' estimates are determined that allow description of individual time profiles.

An analysis will be performed to identify covariates that explain interindividual variability (e.g., but not limited to, CYP3A4 phenotype and T2DM disease status). Covariates reported in published models (27–29) may be included a priori. The PK model will be reported in terms of model parameters (e.g. volumes of distribution, clearances, covariate-relationships) and model derived parameters for exposure (e.g. AUC, t_{max} , C_{max} , C_{trough}). PK parameters will be reported with their residual standard error (RSE) and confidence intervals (CI), as appropriate measures of their uncertainty. Interindividual variability will be reported in terms of coefficient of variation (%CV).

Modeling criteria, goodness of fit and model evaluation

Competing models will be compared based on NONMEM objective function value (OFV), using the likelihood ratio test which compares the difference between log-likelihood for the models (difference in OFV; Δ OFV) to a Chi-square distribution with degrees of freedom corresponding to the difference in number of parameters between the 2 models (e.g. a Δ OFV of -3.84 proves superiority of the new model compared to its parent model at a significance level of 0.05 with one degree of freedom).

Graphical analysis will be used to help assess differences between models. These goodness of fit (GOF) plots include:

- Plots of population predicted concentrations (PRED) versus observed concentrations (DV)
- Plots of individual predicted concentrations (IPRED) versus DV
- Plots of conditional weighted residuals with interaction (CWRESI) versus PRED and versus time
- DV, IPRED, and PRED vs. time
- Histogram and/or QQ plot and/or frequency distribution of the CWRESI
- Histogram and/or QQ plot and/or frequency distribution of the individual specific empirical Bayes' estimates

The predictive performance of the population PK models will be assessed by applying visual predictive checks (VPC).(30)

Software

NONMEM(31) will be used for the nonlinear mixed effect modeling. The NONMEM input file will contain anonymized data and will be created on the remote secure platform. Processing of the model results (tables and graphs) will be performed in R to ensure traceability.(32)

Project Timeline:

Anticipated project start date; one month after data access

Anticipated time for analysis; three months after data access

Anticipated time to manuscript draft; five months after data access

Anticipated time to first manuscript submission; six months after data access

Anticipated time to reporting of the results to YODA; seven months after data access

Dissemination Plan:

Product; The population pharmacokinetic model will be published in a peer-reviewed international journal.

Target audience; Tuberculosis/infectious disease specialists and epidemiologists, and national tuberculosis programs.

Potentially suitable journals; Clinical Infectious Diseases, Clinical Pharmacology and Therapeutics,

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