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2016-0734

General Information

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Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
Project Funding Source: World Health Organisation
yoda_project_coi_form_for_data_requestors_20152.pdf
peter_coi.pdf
richard_coi.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): 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 Resistan
NCT00910871 - A Phase II, Open-label Trial With TMC207 as Part of a Multi-drug Resistant Tuberculosis (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

Safety of Bedaquiline (BDQ) in the treatment of multi-drug resistant tuberculosis: a protocol for an individual patient data meta-analysis

Narrative Summary:
Tuberculosis is a bacterial infection that can affect almost every human organ. It mostly affects the lungs and requires lengthy treatment, for at least 6 months or more. In recent years, strains of of the tuberculosis germ that are resistant to one or more treatments have emerged. More that half a million people are suffering from this multi-drug resistant tuberculosis. A new drug called bedaquiline (BDQ) has been developed and it has been offered exceptionally to some people who would likely die if they received no treatment. We plan to analyse data from the studies in which BDQ was given to patients compared to studies in which it was not given to determine if it is effective and safe.

Scientific Abstract:
Background: Multi-drug resistant tuberculosis (MDR-TB) is a threat to TB control worldwide. There are close to 500,000 cases all around the world. Current treatment regimens include combinations of drugs that are often toxic and which have to be taken for up to 20 months. Treatment success is low. Bedaquiline is a new drug for MDR-TB that has shown promising results in early phase clinical trials and cohorts.
Objectives: To determine the safety, effectiveness and survival rates of patients with MDR-TB who receive BDQ compared to those who don't.
Study design: An individual patient data meta-analysis of BDQ cohorts compared to non-BDQ cohorts.
Main outcome measures: Safety (type, frequency, severity and seriousness of adverse events); Effectiveness (treatment outcomes like cure, sputum conversion at six months) and Survival (mortality rates and causes of death).
Statistical analysis: Baseline covariates will be summarised as counts (percentage) for categorical variables, mean (standard deviation) or median (first quartile, third quartile) for continuous or discrete variables as appropriate depending on the distribution. We will use random-effects logistic regression to determine the effects on safety outcomes among participants who received bedaquiline versus those that did not receive bedaquiline, adjusting for baseline characteristics—in particular, age, sex, HIV status, ethnicity, components of baseline regimen, type of TB, susceptibility to drugs in baseline regimen, associated medical conditions, changes to treatment.

Brief Project Background and Statement of Project Significance:
The emergence of drug-resistant tuberculosis (TB) is a major threat to global TB care and control. In 2014, the World Health Organization (WHO) estimated that 480 000 people developed multidrug-resistant TB (MDR-TB), of which 190 000 died (1). Current treatment regimens for MDR-TB patients are far from satisfactory. These usually require at least 20 months of treatment with a combination of second-line drugs, that are more toxic and less effective than the drugs used to treat drug-susceptible TB (2, 3). In the 2012 global cohort of detected MDR-TB cases, only 50% were successfully treated, as a result of high frequency of death (16%), treatment failure (10%) and loss to follow-up (16%) commonly associated with adverse drug reactions, among other factors. One hundred and five countries have reported at least one case of extensively drug-resistant TB (XDR-TB), a form of MDRTB with additional resistance to fluoroquinolones and second-line injectable drugs (amikacin, kanamycin or capreomycin). On average, an estimated 9.7% of MDR-TB cases have XDR-TB. Treatment options for XDR-TB

patients are even more limited with lower cure rates compared to that of MDR-TB. In a subset of 200 XDR-TB patients in 14 countries, treatment success was achieved in only 33% of the cases while 26% of the patients died (4).
The landscape of drug development for treatment of TB has evolved dramatically over the last ten years, and 6 new compounds are in the final stages of clinical development (1). One of those, bedaquiline, was provided marketing authorisation by the US-FDA under a procedure of “accelerated approval” for the treatment of MDR-TB, in December 2012 (5). Although limited data were available, and the drug had not been tested in a full Phase III randomized controlled trial in humans – but only in a Phase II b trial – in view of the importance of this progress, the likelihood of this drug to contribute effectively to the treatment of a life-threatening disease, and the request by member states to get guidance on the way to use the drug, and following the recommendations of the WHO Guidelines Review Committee (GRC), WHO organised in January 2013 an expert group meeting to review all available data. Based on available knowledge about the safety and efficacy of the product, the evaluation of the balance of potential harms and expected benefit, the target population(s) and the likely conditions of use, in association with the MDR-TB treatment currently recommended by WHO, the expert group advised WHO that the drug may be used under five (5) strict conditions regarding patient inclusion, informed consent, treatment regimen, monitoring of treatment and adequate pharmaco-vigilance. This led to the issuance of an Interim Guidance for the use of bedaquiline in the treatment of MDR-TB in June 2013 (6). Since then, the drug has been registered in a number of countries (including the EU, South Africa, Korea, Russia). WHO estimates that, up to now, the drug has been introduced and used at least once in 46 countries worldwide, under various mechanisms of compassionate use, expanded access programme, donation programmes, import waiver and registered market access (1).

Specific Aims of the Project:
Overall aim:
To re-evaluate the added benefit of bedaquiline to the treatment of MDR-TB, a life-threatening form of tuberculosis, and revise the WHO interim guidance issued in June 2013 in view of updated evidence on its use in conjunction with WHO-recommended MDR-TB treatment regimens.
Specific objectives:
1. To use individual level patient data to evaluate the harms/benefits ratio of bedaquiline in combination with currently recommended MDR-TB treatment regimen according to the following criteria:
(i) for safety, through the evaluation of the type, frequency, severity and seriousness of adverse events related to the use of bedaquiline;
(ii) for effectiveness, through the evaluation of treatment outcomes in cohorts of patients treated with bedaquiline in addition to (optimised) background regimen, in comparison with similar cohorts or programmatically available data;
(iii) for survival, through evaluation of the mortality rates when receiving bedaquiline (and related causes of death).

2. Based on this evaluation, to update the interim guidance on the use of bedaquiline as part of WHO-recommended MDR-TB treatment regimens, as appropriate.

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
New research question to examine treatment safety
Research that confirms or validates previously conducted research on treatment effectiveness
Research that confirms or validates previously conducted research on treatment safety
Summary-level data meta-analysis
Summary-level data meta-analysis will pool data from YODA Project with other additional data sources
Participant-level data meta-analysis
Participant-level data meta-analysis will pool data from YODA Project with other additional data sources

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
Inclusion criteria:
• Humans, no age limit
• Diagnosis of multi-drug resistant tuberculosis (pulmonary and extrapulmonary)
• Bedaquiline added to background MDR-TB regimen for at least 6 months
• Studies implementing drug-monitoring, at least at baseline and at end of treatment
• Individual patient data available
Exclusion criteria:

• Studies not relevant to the main subject (title-screened)
• Studies conducted in animals
• PK-PD studies
• Studies of only-bedaquiline therapy
• Studies not providing information on background therapy (WHO recommended or any other)
• Studies not providing outcome information
• Samples size: Case reports or other observational studies with samples less than 10 participants
• Outcome different to safety and effectiveness
• Quantitative data reports
• Full texts were not available
• Repetitive publications (Duplicates)
• Language limitation (no translation possible by the time of data extraction)

Main Outcome Measure and how it will be categorized/defined for your study:
Main outcome: Safety
Number of adverse events per patient: Numerical
Severity: Mild/moderate/severe
Seriousness: Yes/No
Number with at least one adverse event: Numerical
Number with at least one severe adverse event: Numerical
Number with at least one serious adverse event: Numerical
All events: Yes/No
All adverse event will be categorised by body system and their presence or absence will be qualified as: Yes/no
ECG and lab changes will be collected a numerical continuous data.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The main predictor variable will be the use of Bedaquiline and it will be categorised as a yes/no depending on the study. For TMC 207 it will be categorised at yes.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Age (years), sex (male/female), HIV status (positive, negative, unknown), ethnicity (nominal), components of baseline regimen (standardized/unstandardized), type of TB (pulmonary/extrapulmonary), susceptibility to drugs in baseline regimen (yes/no), associated medical conditions (nominal), changes to treatment (yes/no).

Statistical Analysis Plan:
Descriptive statistics:
Baseline covariates will be summarised as counts (percentage) for categorical variables, mean (standard deviation) or median (first quartile, third quartile) for continuous or discrete variables as appropriate depending on the distribution. Baseline covariates and outcomes will be analysed individually for each cohort, and then according to the presence or absence of bedaquiline.
Primary analysis:
We will use random-effects logistic regression to determine the effects on safety outcomes among participants who received bedaquiline versus those that did not receive bedaquiline, adjusting for baseline characteristics—in particular, age, sex, HIV status, ethnicity, components of baseline regimen, type of TB, susceptibility to drugs in baseline regimen, associated medical conditions, changes to treatment. In this analysis, study will be used as a random-effect. For this analysis we will use the PETTS study as the comparator group (12) because it is a more homogenous cohort in terms of participants, interventions, outcomes and follow-up time. These analyses will be replicated for the effectiveness and survival outcomes—with the latter based on random-effects Cox-regression approach.
Sensitivity analysis:
In order to test the robustness of our analyses, we will repeat the analysis using the Ahuja et al study as a comparator group. It is a more heterogeneous data set including 32 cohorts (9898 patients) from different countries. (11)
Subgroup analyses:
We will investigate subgroup effects by introducing interaction terms into our models for age, sex, HIV status, type and severity of TB.

Project Timeline:
Data analysis: 8 Feb to 18 March 2016.
Report writing: 18 March to 21 March 2016.
Discussion with guideline development group (WHO): 23 to 31 March 2016.
Experts meeting (WHO): 11-15 April 2016.

Dissemination Plan:
The results will be disseminated as WHO reports and as peer reviewed publications (JAMA, Lancet, BMJ).

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Supplementary Material: bdq_protocol_10.02.2016.pdf