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General Information

Key Personnel (in addition to PI): **First Name:** Zhiyi
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Primary Affiliation: McGill University

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: American Thoracic Society, US Centers for Disease Control and Prevention, Infectious Diseases Society of America, and European Respiratory Society

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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

Determinants of treatment outcomes of multidrug-resistant tuberculosis (MDR-TB): an Individual Patient Data (IPD) Meta-Analysis - Update

Narrative Summary:
Multidrug-resistant tuberculosis (MDR-TB) infection is associated with long treatment duration, use of toxic drugs, and generally poor outcomes. Newer TB drugs has been used in recent years to treat MDR-TB. In order to update the evidence for treatment recommendations of MDR-TB, we are planning to obtain and meta-analyze individual patient data from all recent MDR-TB studies, and identify the treatment correlates of successful outcomes of MDR-TB.

Scientific Abstract:
Background: Multidrug-resistant tuberculosis (MDR-TB) infection is associated with long treatment duration, use of toxic drugs, and generally poor outcomes. Individual patient data meta-analysis can be used to identify the treatment correlates of successful outcomes of MDR-TB, and update the current recommendation for MDR-TB treatment.
Objective: Conduct an updated individual patient data (IPD) meta-analysis of patients who were treated for MDR-TB to determine treatment correlates with treatment outcomes.
Study Design: Systematic review has been performed to identify the studies that reported MDR-TB treatment regimens and outcomes since January 2009. Study authors will be contacted to ask for sharing individual patient data for each study. All datasets from different centers will be assembled into one database, and data will be meta-analyzed to identify determinants of treatment outcomes of multidrug-resistant tuberculosis.
Participants: Microbiologically confirmed MDR-TB patients reported in eligible studies published since January 2009 in peer-reviewed / indexed journals
Main Outcome Measures: end-of-treatment outcomes (cure, treatment completed, death, treatment default, treatment failure, transfer out & relapse); time to sputum culture conversion; adverse events.
Statistical Analysis: Individual patient data meta-analysis using random effects model

Brief Project Background and Statement of Project Significance:
Multidrug-resistant tuberculosis (MDR-TB), defined as tuberculosis resistant to at least isoniazid (INH) and rifampin (RIF), has become a major threat to global tuberculosis control in recent years. MDR-TB requires prolonged treatment with a combination of multiple second line drugs which are more toxic and yet less effective than first line drugs. Treatment outcomes are poor and there is considerable controversy regarding the best treatment regimen – largely because of inadequate evidence to support current treatment recommendations.
In 2009, WHO issued a call for evidence to draft new recommendations for treatment of MDR-TB. Initially, 3 systematic reviews were completed and meta-analyzed the data of eligible literatures [1-3]. However, identification of optimal treatment regimens was extremely difficult as pooling of results across studies was limited by the complexity of the patients' characteristics and individualized treatment. To address this problem, we (the McGill group) conducted an individual patient data (IPD) study in 2010, and a data base was assembled of individual patient records from almost 10,000 MDR-TB patients from 32 centers of 20 countries [4].
This rich data base has allowed seven distinct set of analyses to address different important questions regarding interpretation of DST, role of surgery, prognosis and correlates of treatment success of MDR-TB. Meta-analysis of this data set produced the majority of evidence which the WHO expert committee used to make new recommendations for MDR-TB treatment published in 2011 [5]. Five papers (one in PLoS Medicine, two in ERJ, and two in CID) have been published so far and the results have influenced several sets of WHO recommendations [4, 6-10].
In the past five years, newer TB drugs has been used to treat MDR-TB patients, including later generation fluoroquinolones, linezolid, clofazimine, delamanid, and bedaquiline. US Centers for Disease Control and Prevention (CDC), American Thoracic Society (ATS) and Infectious Diseases Society of America (IDSA) plan to issue revised guidelines for treatment of MDR-TB and other forms of drug resistant TB in the fall of 2016. They approached us at McGill to update the IPD in MDR-TB with a particular emphasis on these newer drugs. Therefore, we (the McGill group), in collaboration with ATS/CDC/IDSA, will conduct an updated IPD study in order to generate evidence to update the current MDR-TB treatment recommendations. Authors of eligible publications from Jan. 2009 will be contacted and asked for participation in this study. An updated data base will be assembled and

individual patient data will be analyzed to address major questions regarding MDR-TB treatment.

Specific Aims of the Project:
Conduct an updated individual patient data (IPD) meta-analysis of patients who were treated for MDR-TB to determine treatment correlates with treatment outcomes.
We will have a particular focus on certain drugs, for which we believe there is significant new evidence from recently published studies:
• High-dose isoniazid
• Later generation fluoroquinolone
• Linezolid
• Clofazimine
• Bedaquiline
• Delamanid
• Carbapenems

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
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:
Data source of the study:
Individual patient data from eligible studies that reported MDR-TB treatment regimens and outcomes, published since January 2009 in peer-reviewed / indexed journals
Inclusion criteria:
1) Studies published since January 2009 in peer-reviewed / indexed journals. A systematic review has been conducted by investigators at McGill University to identify the eligible studies.
2) MDR-TB is bacteriologic confirmed (phenotypic or genotypic)
3) Patients with pulmonary MDR-TB. Extra pulmonary MDR-TB patients could also be included and this could be a secondary objective for later analysis.
4) Adults (age definition may vary but at minimum age ? 12)
5) The study reported at least 25 patients with MDR-TB
6) The study must report at least one of the following outcomes: end-of-treatment outcomes, time to culture conversion, or adverse events.
Exclusion criteria:
1) Studies published only as grey literature will be excluded
2) Studies describing the results of treatment with regimens of less than 12 months will not be included

Main Outcome Measure and how it will be categorized/defined for your study:
The primary outcome assessed will be:
1) End-of-treatment outcomes: Cure, Treatment complete, Death, Treatment default, Treatment failure, Transfer out (& relapse if measured). These will be defined by Laserson et al., 2005 [11].
Additional outcomes assessed will be:
2) Time to culture conversion, defined as the months/days that a patient achieved sputum conversion from the start of the treatment.
3) Adverse events (AEs). We are particular interested in serious AE that is classified as grade 3-4 or leads to drug permanently discontinued. Identifying the drug responsible for AEs is also important for the analysis.

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
Treatment regimens for MDR-TB:
1) Drugs used in intensive phase (drug names and dosage)
2) Duration of intensive phase

3) Drugs used in continuation phase (drug names and dosage)
4) Duration of continuation phase
5) Surgery: whether surgery was performed for MDR-TB treatment, and when surgery was performed

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
Demographic and clinical information at diagnosis:
1) Age: the age of MDR-TB patient
2) Gender: male or female
3) Height, weight and BMI
4) Smoking: current smoker, ex-smoker, non-smoker or unknown.
5) HIV status: whether the patient was HIV positive
6) ART information: if the patient was HIV positive, whether he/she received antiretroviral therapy
7) Diabetes: whether the patient had diabetes
8) Prior first-line TB treatment history: whether the patient had prior TB treatment history with first line drugs only
9) Prior second-line TB treatment history: whether the patient had prior TB treatment history with second line TB drugs
10) Cavitary disease: whether the patient had cavitary disease based on chest x-ray results
12) Bilateral disease: whether the patient had bilateral disease based on chest x-ray results
13) Acid-Fast Bacilli (AFB) Smear results: whether the patient is AFB smear positive
14) Drug susceptibility testing (DST) results for all drugs tested

Statistical Analysis Plan:
All individual patient datasets (including the requested clinical trial data through YODA project, and datasets from other studies) will be merged into one file and analyzed using SAS. Three types of drug-exposure will be considered in our meta-analysis: (i) specific drugs administered, (ii) duration of treatment regimen, and (iii) number of likely effective drugs used. Drugs are considered likely effective if susceptible on drug susceptibility testing, regardless of history of prior use. We will estimate odds of treatment success (defined as treatment cure or completion) compared to one of three alternate outcomes: (i) treatment failure or relapse; (ii) treatment failure, relapse or death; and (iii) treatment failure, relapse, death or default.
We will use random effects (random intercept and random slope) multi-variable logistic regression estimated via penalized quasi-likelihood (Proc Glimmix in SAS [12]) in order to estimate the adjusted odds and 95% CIs of treatment success associated with different treatment covariates [13-15]. As a sensitivity analysis, all models for primary analyses will also be estimated using adaptive quadrature (QUAD) [16]. Patients will be considered as clustered within studies and intercepts and slopes of the main exposure variables will be allowed to vary across studies; this is to account for otherwise unmeasured inter-study differences in patient populations, as well as center-specific differences in data ascertainment, measurement, and other factors. The variance of the study specific intercepts (here the baseline log odds of success in each cohort) and slopes (here treatment efficacy) will be interpreted to indicate how much these varied across the studies. We will report the average estimate of effect across studies from these models and the estimate inter-study variability and standard deviation of that variance, as well as the variance of the intercept and the standard deviation of that variance. Estimates of effect of each treatment parameter for each dataset will be adjusted for covariates: age, gender, HIV co-infection, AFB smear results, and past history of TB treatment, etc.
In addition to a traditional multivariable model, we will also use a propensity score–based method for adjusting for potential confounding [17].
Heterogeneity will also be explored visually using Forest plots of study specific estimates, and estimated quantitatively via the I2 and its associated 95% CI [15]. For these analyses, estimates of effect will be calculated separately for each study, adjusting for relevant patient-level covariates, and pooled using conventional meta-analytic techniques.

Project Timeline:
Project start date: January, 2016 (already started)
All datasets from different participating centers collected (including the two RCT data requested through YODA project): By the end of April, 2016
Assemble all datasets from different centers into one data base for analysis: by May, 2016
Preliminary analysis completion date: by August, 2016
Final analysis completion date: by February, 2017
Date manuscript drafted and first submitted for publication: by August, 2017
Date results reported back to the YODA Project: at the same time when first paper is submitted for publication

(extension of the agreement may be needed).

Dissemination Plan:
Anticipated products:
• ATS/CDC/IDSA updated treatment guideline for MDR-TB
• Possibly updated WHO guideline for MDR-TB treatment
• Publications in peer-reviewed journals
Potential suitable journals for submission:
• Clinical Infectious Diseases
• European Respiratory Journal
• PLOS Medicine
Target audiences:
• Health professionals and researchers involved in MDR-TB treatment

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Supplementary Material: protocol_update_ipdinmdr.pdf
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