Principal Investigator

First Name: Gustavo
Last Name: Velásquez
Degree: MD, MPH
Primary Affiliation: Brigham and Women's Hospital
E-mail: gvelasqu@post.harvard.edu
Phone number: 617.732.8881
Address: 15 Francis St, PBB-A4

City: Boston
State or Province: MA
Zip or Postal Code: 02115
Country: USA
SCOPUS ID: 46761561000

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General Information

Key Personnel (in addition to PI): **First Name:** Megan B.
Last name: Murray
Degree: MD, MPH, ScD
Primary Affiliation: Harvard Medical School

First Name: Carole D.
Last name: Mitnick
Degree: ScD
Primary Affiliation: Harvard Medical School

First Name: Sonia
Last name: Hernández-Díaz
Degree: MD, MPH, DrPH
Primary Affiliation: Harvard T.H. Chan School of Public Health

First Name: Sidney S.
Last name: Atwood
Degree: BA
Primary Affiliation: Brigham and Women's Hospital

Are external grants or funds being used to support this research?: External grants or funds are being used to support this research.
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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
What type of data are you looking for?: Individual Participant-Level Data, which includes Full CSR and all supporting documentation

Research Proposal

Project Title

Estimating the effect of bedaquiline on MDR-TB culture conversion and treatment outcomes using marginal structural models

Narrative Summary:
This project will use a new analytical method – marginal structural Cox proportional hazards modeling with inverse probability weighting – to reanalyze the time to culture conversion and final World Health Organization treatment outcomes for NCT00449644, the Phase IIb trial where participants with newly diagnosed, smear-positive, multidrug-resistant tuberculosis (MDR-TB) were randomized to receive either bedaquiline or placebo, both in combination with a preferred background regimen for MDR-TB. Using these methods, we will adjust for differential adherence and loss to follow-up between the treatment groups, and report new adjusted estimates for these efficacy endpoints.

Scientific Abstract:
Background: Randomized clinical trials evaluating the comparative efficacy of multidrug-resistant tuberculosis (MDR-TB) treatment regimens against an active comparator are susceptible to post-randomization bias from differential adherence and loss to follow-up (1,2). In NCT00449644, the Phase IIb trial where participants were randomized to receive bedaquiline versus placebo, both in combination with a preferred background regimen for MDR-TB, the experimental arm had 23% withdrawal at 120 weeks compared with 35% in the placebo arm, based on World Health Organization (WHO) treatment outcome definitions (3).
Objective: To obtain valid estimates of the comparative efficacy of MDR-TB treatment regimens.
Study Design: We will first replicate the original trial findings by estimating the time to culture conversion and WHO treatment outcomes using traditional Cox proportional hazards models. We will then use marginal structural Cox proportional hazards models with inverse probability weighting to adjust for differential adherence and loss to follow-up, and report new adjusted estimates for these efficacy endpoints.
Participants: Newly diagnosed, sputum smear-positive, pulmonary MDR-TB participants in the modified intention-to-treat population from NCT00449644.
Main Outcome Measure(s): New effect estimates for time to sputum culture conversion and WHO treatment outcomes reported for NCT00449644, adjusted for differential adherence and loss to follow-up.
Statistical Analysis: Marginal structural Cox proportional hazards modeling with inverse probability weighting.

Brief Project Background and Statement of Project Significance:
Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis with in vitro resistance to the two most potent antituberculous drugs, isoniazid (INH) and rifampin (RIF). Current available treatment for MDR-TB is longer, more

expensive, and more toxic than treatment for susceptible strains (4), and associated with only 48% treatment success globally (5). Access to MDR-TB treatment is limited, with only 20.2% of the estimated 480,000 incident MDR-TB cases in 2013 started on treatment (5). Two new antituberculous drugs, bedaquiline and delamanid, have recently been approved for MDR-TB treatment when no other options are available (6,7); these drugs are currently being investigated in Phase III trials (8).

Randomized clinical trials evaluating the comparative efficacy of MDR-TB treatment regimens against an active comparator of standard-of-care are susceptible to post-randomization bias from differential adherence or loss to follow-up (1,2). Overall, 23% default has been reported among patients receiving traditional MDR-TB regimens, in the largest individual patient data meta-analysis of MDR-TB outcomes to date (9). In NCT00449644, the Phase IIb trial where participants were randomized to receive bedaquiline versus placebo, both in combination with a preferred background regimen for MDR-TB, the experimental arm had 23% withdrawal at 120 weeks compared with 35% in the placebo arm, based on a post-hoc analysis using World Health Organization (WHO) treatment outcome definitions (3). Post-randomization bias may therefore be a challenge to the analysis of trials comparing novel MDR-TB regimens to standard-of-care controls, both now and in the future.

Advances in the field of causal inference have translated into the use the successful application of inverse probability weighting methods in the fields of HIV therapy (10-12) and occupational medicine (13,14). Unlike standard analytical methods, inverse probability weighting methods can appropriately adjust for time-varying covariates that are simultaneously confounders and intermediate variables (11). These methods yield unbiased estimates of causal effects by creating a “pseudopopulation” where the effect estimate is equal to a situation in which nobody was censored (15).

This proposal is innovative because, to our knowledge, inverse probability weighting methods have not been previously applied to MDR-TB comparative effectiveness research. This project is significant because we will mitigate salient biases in the reporting of bedaquiline effect estimates, and we plan to use lessons learned from this analysis to standardize the application of inverse probability weighting methods for future analyses of MDR-TB outcomes within clinical trial settings.

Specific Aims of the Project:
The objective of this study is to use marginal structural Cox proportional hazards models with inverse probability weighting to reanalyze the primary (time to culture conversion) and secondary (WHO treatment outcome) efficacy endpoints for NCT00449644, the Phase IIb bedaquiline trial. Our hypothesis is that new effect estimates adjusted for differential adherence and loss to follow-up obtained using these methods will be attenuated when compared to previously published estimates.

What is the purpose of the analysis being proposed? Please select all that apply. Research that confirms or validates previously conducted research on treatment effectiveness
Preliminary research to be used as part of a grant proposal

Research Methods

Data Source and Inclusion/Exclusion Criteria to be used to define the patient sample for your study:
The patient sample for this analysis will be the modified intention-to-treat population from NCT00449644 (3). Inclusion criteria were ages 18 to 65 and newly diagnosed, sputum smear-positive, pulmonary MDR-TB based on proportion-methods or rapid-screening tests. Exclusion criteria were previous MDR-TB treatment, HIV with CD4 <300, complicated or severe extrapulmonary or neurologic TB, severe cardiac arrhythmia requiring medication, corrected QT >450 msec using Fridericia’s formula, history of risk factors for torsades, concomitant serious illness, alcohol or drug abuse, pregnancy or breastfeeding, and previous treatment with bedaquiline. The modified intention-to-treat exclusion criteria were no positive mycobacterial cultures from sputum samples obtained before administration of the first dose of the study drug or a positive culture up to week 8 in cases in which baseline cultures were negative, those for whom susceptibility to rifampin and isoniazid was shown or resistance could not be confirmed, extensively drug-resistant tuberculosis (XDR-TB), and those who had not undergone assessment after baseline (3).

Main Outcome Measure and how it will be categorized/defined for your study:
The outcome measures for this analysis will be updated effect estimates for the primary (time to culture conversion)

and secondary (WHO treatment outcome) efficacy endpoints reported for NCT00449644 (3), adjusted for differential adherence and loss to follow-up. The primary outcome will be time to sputum culture conversion during treatment with bedaquiline or placebo, defined as the interval in days between the date of treatment initiation and the first of two consecutive negative cultures from sputa collected at least 28 days apart, with all intermediate cultures negative. The secondary outcome will be adapted consensus WHO MDR-TB treatment outcome definitions as specified in the study protocol (3,16).

Main Predictor/Independent Variable and how it will be categorized/defined for your study:
The main independent variable is randomization to receive bedaquiline (400mg once daily for 2 weeks, followed by 200mg three times a week for 22 weeks, administered as 100mg tablets) or placebo, both in combination with a preferred five-drug, second-line antituberculosis background regimen for MDR-TB. As per the study protocol (3), the intention-to-treat (ITT) population includes all subjects, regardless of their compliance with the protocol, who had at least 1 intake of bedaquiline or placebo. The modified ITT population (protocol-defined efficacy population) excludes all subjects from the ITT population who turned out to have XDR-TB or non-MDR-TB based on the susceptibility results from samples taken prior to randomization.

Other Variables of Interest that will be used in your analysis and how they will be categorized/defined for your study:
The randomization of participants to receive bedaquiline versus placebo was stratified by trial site and degree of lung cavitation defined as the presence of at least one cavity ?2 cm (i.e., no cavity, cavitation in one lung, or cavitation in both lungs). We will adjust for these two stratification variables to replicate the original trial findings (3). We will also perform secondary analyses as published in the original trial: 1) the same analysis in the full intention-to-treat population; and 2) the modified intention-to-treat population analysis further adjusting for unequally distributed baseline factors (pyrazinamide resistance, HIV status, and baseline albumin grade, with the exception of pre-XDR-TB due to a small 7% between-group difference).

Statistical Analysis Plan:
We will first replicate the original trial findings for NCT00449644 by estimating the primary (time to culture conversion) and secondary (WHO treatment outcome) efficacy endpoints comparing the treatment groups in the modified intention-to-treat population using traditional Cox proportional hazards models. The stratification variables, degree of lung cavitation and trial center, will be used as covariates in these models as in the original published trial. We will also perform secondary analyses in the modified intention-to-treat population further adjusting for unequally distributed baseline factors, and in the full intention-to-treat population.

We will then use marginal structural Cox proportional hazards models with inverse probability weighting to adjust for differential adherence and loss to follow-up, and report new adjusted hazard estimates comparing the treatment groups with respect to time to culture conversion and individual WHO treatment outcomes. We will do this by analyzing each month of treatment using stabilized weights to obtain an inverse probability-of-treatment-and-censoring weight partial likelihood estimate (17). We will also construct Kaplan-Meier curves for graphical comparison of the published trial findings and the findings from inverse probability weighting across treatment groups.

Project Timeline:
Anticipated project start date: One month after trial data access.

Anticipated time for statistical analysis: Six months after trial data access.

Anticipated time to manuscript draft: Eight months after trial data access.

Anticipated time to first manuscript submission for publication: Nine months after trial data access.

Anticipated time to reporting of results to the YODA project: Ten months after trial data access.

Dissemination Plan:
Anticipated products: One peer-reviewed manuscript and one conference presentation.

Anticipated target audience: Tuberculosis/infectious disease specialists and epidemiologists, and national tuberculosis programs.

Potentially suitable conferences for presentation of research project: Union World Conference on Lung Health, IDWeek.

Potentially suitable journals for submission of the completed research project: New England Journal of Medicine, American Journal of Respiratory and Critical Care Medicine, Clinical Infectious Diseases.

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