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The IDEAL trial - a study protocol for a phase III randomized, double-blinded clinical trial assessing the ultra-short antibiotic prophylaxis of Isoniazid and Rifapentine in non-immunosuppressed patients with newly diagnosed latent tuberculosis

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Abstract:

Introduction: Tuberculosis (TB) is a global infectious disease that has plagued human beings for centuries. It currently ranks as one of the primary causes of death by a single agent. Treatment of latent TB (LTBI) is one of the cornerstones used to prevent the activation of TB. The current regimens are lengthy, associated with poor treatment adherence and several side effects. The need for shorter regimens is essential to control TB infection and accomplish the "End TB Strategy," which has been proclaimed by the World Health Organization (WHO). Our study aims to provide a study design that assesses the efficacy of one month of Isoniazid (IHN) and Rifapentine (RFT) in non-immunosuppressed LTBI patients.

Methods: The proposed study will be a phase III, single-center, randomized, two-arms (1:1 ratio), double-blinded, placebo-controlled non-inferiority trial. We will include immunocompetent patients above the age of 18 with a new diagnosis of LTBI. Participants will be randomized, either receiving one month of INH with RFT or 6 months of INH alone with respective placebo to maintain blinding. The primary study outcome is the cumulative incidence of active TB in the studied treatment arms. The secondary outcome is the cumulative incidence and severity of adverse effects of the studied regimens.

Discussion: Given the scope and spread of LTBI around the globe, shorter and safer treatment options are of the utmost importance to eradicate TB. The proposed trial can contribute to this objective by improving the current standard of care. Potential disadvantages of the trial design include the need for many participants, trial duration and costs.

Keywords: Tuberculosis, latent infection, prophylaxis, rifapentine, isoniazid

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INTRODUCTION

Tuberculosis (TB) is a bacterial infection that has been one of the leading causes of death worldwide, despite the discovery of effective and affordable antibiotics more than 50 years ago (Floyd, Raviglione, & Glaziou, 2018). Today, one-fourth of the world's population is infected with TB (Floyd et al., 2018). In 2018, 10 million people around the world became infected with TB, and 1.5 million TB-related deaths occurred worldwide (WHO,

2019). TB has recently been classified as the tenth most common global cause of death and remains the leading cause of death by a single infectious agent, symbolizing a significant public health burden, especially in poorly developed countries (Floyd et al., 2018; WHO, 2016).

Typically, in immunocompetent hosts, the bacterial replication is controlled by the immune system. This bacterial recurrence leads to an asymptomatic state of infection known as latent TB infection (LTBI) (Houben & Dodd, 2016). During latent infection, a dynamic balance

between the bacteria and host immune responses is established, and any event that weakens cell-mediated immunity may lead to active bacterial replication, systemic infection, and disease activation, commonly known as active TB (Delogu, Sali, & Fadda, 2013). On average, 5 to 10% of people with LTBI will transition to active TB disease during their lifetime without treatment. In this group, patients without immunosuppression have a risk of 50% of developing an active TB during the first two years following the initial infection (Ai, Ruan, Liu, & Zhang, 2016; Haley, 2017; Salgame, Geadas, Collins, Jones-Lopez, & Ellner, 2015). The risk is more prevalent in people with HIV, diabetes, or other conditions that affect the immune system (Swindells et al., 2019).

For this reason, a variety of anti-tuberculosis treatment regimens have been evaluated in the management of LTBI, aiming to eradicate TB and to reduce the likelihood of subsequent disease reactivation (Denholm, 2010). In addition to early identification and treatment of active TB cases, TB elimination is most likely to be achieved if LTBI is treated consequently (CDC, 2018). Currently, various established treatment regimens for LTBI use isoniazid (INH), rifapentine (RFT), rifampicin (RIF), or a combination of them. LTBI treatment, however, faces various problems including (I) the significant lack of resources for the management of patients in poorly developed countries (WHO, 2019), (II) the inappropriate use of LTBI treatment regimens among patients' close contacts (WHO, 2018), (III) the refusal of patients to take treatments for an asymptomatic condition (Fox, Dobler, Marais, & Denholm, 2017), (IV) and the low compliance due to adverse effects (Blumberg & Ernst, 2016). Other substantial problems are the reluctance of healthcare professionals to initiate preventive therapies due to their lack of knowledge and the fear of the appearance of side effects (Paton et al., 2019). INH monotherapy has been the most established and widely used drug to treat LTBI for decades (Holland & Norton, 2012). However, the high efficacy of the 6 to 12-month treatments of INH alone is affected by the low rates of compliance and increased risks of adverse events, such as hepatotoxicity (Hirsch-Moverman Y., 2008; Huaman, 2019; Kopanoff, 1978). Shorter treatments were proposed and proved to have similar efficacy with higher compliance rates and fewer adverse events (Comstock, 1999; Tang & Johnston, 2017). Overall, shorter regimens are preferred by participants as they increase treatment adherence (Comstock, 1999; Tang & Johnston, 2017). The combination of INH and RFT has been of recent interest in the treatment of LTBI. A recent study proved the effectiveness of an ultra-short LTBI treatment regimen consisting of INH and RFT

administered for only one month (Swindells et al., 2019). Considering the enormous benefits of proving an ultra-short LTBI treatment to be effective, we propose a trial design to investigate the effectiveness of a one-month treatment with INH and RFT in non-immunosuppressed patients.

DESIGN AND METHODS

Study Aim

Given the proven effectiveness of this ultra-short antibiotic treatment in immunosuppressed patients, this trial aims to verify the usefulness of the regimen in non-immunosuppressed LTBI patients.

Study design

This is a phase III clinical trial protocol of a planned single-center, randomized, double-blinded, placebo-controlled (double dummy), two arms, non-inferiority study assessing the ultra-short antibiotic prophylaxis of INH and RFT in non-immunosuppressed patients with LTBI. The follow-up time is two years starting from the first drug administration.

Study arms and intervention

The planned trial has two study arms (figure 1). The experimental arm will receive daily RFT and INH for the first month, followed by five months of INH placebo. The control arm will receive INH and RFT placebo during the first month, followed by five months of INH alone. RFT and INH doses will be administered according to body weight. After informed consent, randomization and enrollment, the study participants will be screened undergoing clinical evaluation, chest x-ray, and lab testing, including QuantiFERON blood testing (QFT), complete blood count (CBC), and liver enzymes measures. During the trial, the participants will be clinically evaluated monthly for the first 6 months and will undergo lab testing (CBC and liver enzymes) during every visit. They will also undergo an evaluation with lab testing (CBC and liver enzymes) after 12 months. The final review, after two years, will also include chest x-ray plus lab testing (QFT, CBC, and liver enzymes) (figure 1).

Study setting

The study will be conducted in Qatar. This country has a well-structured national TB program that aims to eliminate active TB cases by 2030. Today, Qatar has a TB incidence of 31 out of 100.000 per year (WHO, 2019). Due to the TB eradication policy, all new immigrants to Qatar will be screened for active TB and LTBI (including

Timeline

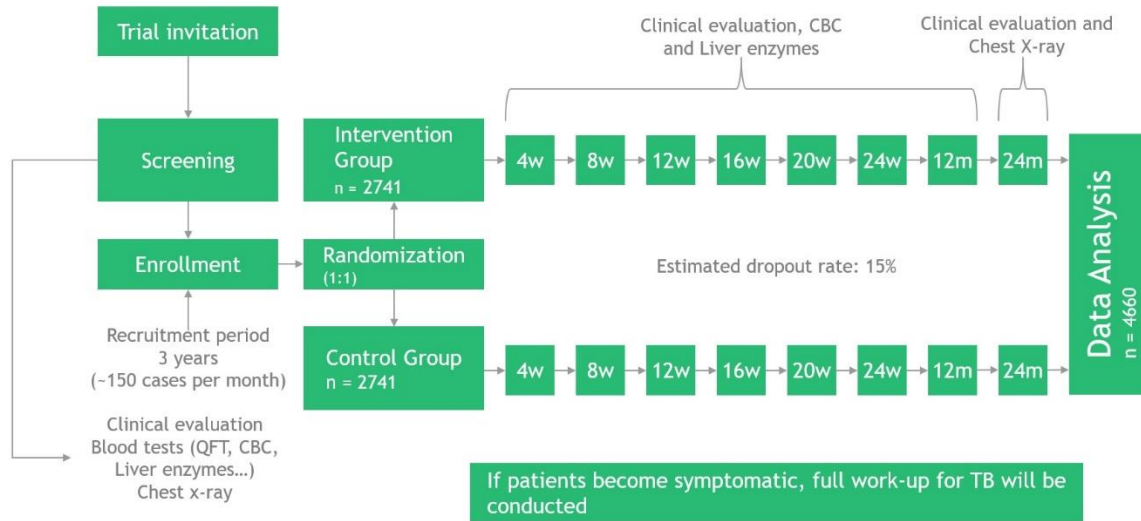


Figure 1. Flowchart and study arms (w = weeks, m = months).

patients coming from endemic countries, medical students, healthcare workers, laborers, prisoners, etc.). Should the participants have active TB or LTBI, they will receive antibiotic treatment. The Communicable Diseases Center (CDC) is the only reference hospital for all TB cases in Qatar (LTBI and active TB) and runs 10 TB clinics a day. In 2018, nearly 11,500 people were screened for TB. The screening identified 300-400 new cases of LTBI a month. Most immigrants come from endemic TB regions like Southeast Asia, Eastern Europe and Southeast Africa and work in construction sites for a limited time of two years. All patients with active TB or LTBI receive the appropriate TB treatment with Direct Observed Therapy (DOT). The DOT is delivered either by daily visit at the CDC, regular home visits, or video-assisted DOT. Given these factors, the CDC Qatar provides the necessary infrastructure to conduct the proposed trial successfully.

Sample size

The sample size calculation considered the following variables: an expected event rate in the control group of 1.5%; an expected difference in event rates between groups of 0.1%; a non-inferiority margin of 1%; a dropout rate of 15%; and 1:1 allocation. The event rate of 1.5% under 6 months of INH was estimated based on historical data (Sterling et al., 2011). The difference in event rates between groups is expected to be near zero (0.1%) based on the results of a similar trial (Swindells et al., 2019). The established non-inferiority margin of 1% is consistent

with previous studies (Sterling et al., 2011; Swindells et al., 2019). With these assumptions and variables, we calculated that 5482 study subjects need to be enrolled, of whom 4660 will be included in the final analysis (after dropouts) to maintain an 80% statistical power and a one-sided type I error rate of 5%.

Recruitment

Considering the unique circumstances at the CDC Qatar (see "Study setting"), the recruitment process is planned to occur over three years, enrolling 150 study subjects per month. The use of advertisement and recruitment materials such as flyers, phone calls, and social networks will help facilitate recruitment rates. Leaflets and posters will address nongovernmental organizations and tuberculosis patient groups.

Eligibility criteria

Patients age 18 or above with a confirmed LTBI diagnosis will be included (based on clinical evaluation, QuantiFERON-TB Gold Plus (QFT), and chest x-ray). A chest x-ray must be negative for active TB. All patients, following a consideration period of at least 24 hours, must be able to fully understand the necessary trial information and sign the informed consent form before study enrollment. Patients will be excluded due to pregnancy, breast-feeding, immunosuppression, or a body weight of ≤ 30 kg. TB treatment in the past two years, elevated liver enzyme levels or hepatic or renal

dysfunction, as well as patients who receive drugs that interfere with cytochrome enzymes, will be excluded. Patients undergoing chemotherapy, radiotherapy, or immunotherapy for malignancies will not be enrolled in the trial.

Randomization

Simple randomization with a 1:1 allocation will be utilized. Randomization will be conducted using the 'Castor' tool, a cloud-based online randomization tool (Castor-CDC, 2019). The physicians will receive the treatment of the assigned subject according to this platform. Involved physicians will only have access to the supervised subjects' regimen information but not the allocation.

Blinding

Only safety officers, the data safety monitoring board (DSMB), and dispensing pharmacists will remain unblinded throughout the study. Control arm participants will receive a daily placebo of RFT during the first month of treatment. Intervention arm participants, on the other hand, will receive a daily placebo of INH after the first month until the end of the drug administration after a total of six months. RFT placebo pills will include red dye to mimic red urine discoloration during RFT administration in the experimental arm to prevent unintentional unblinding.

Outcomes

Primary outcome

The primary study outcome is the cumulative incidence of active TB after two years of the studied regimens. Symptoms for active TB will be assessed in all visits. Symptomatic participants will undergo a chest x-ray. In the case that the image suggests pulmonary TB, three sputum samples will be collected to confirm active TB. At the final visit after 24 months, a chest x-ray will be performed on all subjects, regardless of clinical symptoms.

Secondary outcome

The secondary outcome is the cumulative incidence and severity of the adverse effects of the studied regimens. Groups will be compared in terms of the incidence rates of each adverse event and the rates of combined unexpected adverse events.

Data management and monitoring

An external Data Monitoring Committee (eDMC) will monitor the data from this study. The voting members of the committee are external. The members of the eDMC

must not be involved with the research in any other way (i.e., they cannot be study investigators) and must have no conflict of interests that could affect their roles concerning the study. The eDMC will make recommendations to the principal investigator regarding steps to ensure both the participants' safety and the continued ethical integrity of the study. Moreover, the eDMC will consider the overall risk and benefit for study participants and will determine whether the investigation should continue per the proposed protocol.

Interim analyses

Given the novelty of the experimental treatment regimen, the eDMC will analyze the data at regular intervals to warrant participants' safety. The first one will be performed after three months of the trial and the following analyses are going to be performed every three months thereafter in the first year and every six months throughout the following years. The eDMC has a general responsibility to safeguard the interests of the subjects by monitoring safety through the described interim analyses. An Independent Statistical Analysis Center (ISAC) will support the eDMC throughout the entire course of the trial and will carry out the formal interim analysis. The eDMC will also make appropriate recommendations based on the outcomes of every analysis.

Statistical analysis

As both outcomes are categorical, we are going to use the Chi-Square-test for proportions comparison, considering a significance level of 0.05. The study utilizes a modified intention to treat analysis - analysis will include every participant who receives at least the initial dose of the experimental or control arm regimen. The difference in primary outcome rate will be presented alongside a 95% confidence interval (CI). If the upper limit of the 95% CI for the difference in overall response is below 1%, non-inferiority will be concluded. Moreover, a comparison of baseline characteristics will be made using Z-scores. If a significant difference is detected, a logistic regression analysis will be performed subsequently. Finally, a comparison of dropout rates will be conducted. If a discrepancy is detected, a secondary analysis will be done. All analyses will be conducted using STATA 15.1. (StataCorp, College Station, TX, USA).

Ethical and legal requirements

This protocol will be submitted to the institutional review board of the CDC Qatar. Also, necessary changes and

adjustments will be implemented accordingly. The study will be registered on www.clinicaltrials.gov.

DISCUSSION

TB and LTBI still represent global public health challenges and are significant causes of infectious disease-associated morbidity and mortality. Thus, standard, short, and tolerable treatment regimens are needed to improve TB prevention and, ultimately, achieve disease eradication as aspired by the WHO (WHO, 2015). Hence, sufficient LTBI treatments are essential. Albeit there are established and effective treatment regimens available, most of them are lengthy and often cause considerable adverse effects. This resource intensity and subsequent constraints in patient adherence deny pleasing treatment results. Herein, we provide a study protocol aiming to improve the standard of care for LTBI by investigating the effectiveness of an ultra-short antibiotic treatment with INH and RFT.

The proposed study addresses the outlined problems about the current standard of care for non-immunosuppressed patients with LTBI. Despite the estimated high costs, large sample size, and length of the trial, our study remains feasible considering the specific advantages given at the CDC Qatar. Moreover, the chances of proving the chosen ultra-short antibiotic regimen to be effective are relatively high, considering recent findings (Swindells et al., 2019). A potential limitation of LTBI trials, in general, is the rarity of observed events, namely the development of active TB in treated LTBI patients. Thus, choosing a reasonable non-inferiority margin and event difference rate are challenging because of the lack of information in specific patient populations, treatments, and due to varying patient risk factors (Haley, 2017; Sterling et al., 2011). This issue can significantly impact the statistical outcomes of the proposed trial. Moreover, it is unclear how the heterogeneity of the investigated patient population at the CDC Qatar will impact study findings. Yet, data of this trial could provide valuable insights and might help develop more effective LTBI trials for specific subpopulations and other regimens in the future. This study, overall, could advance the standard of care for LTBI patients around the globe by leveraging a shorter, safer, and effective antibiotic treatment.

CONCLUSIONS

Considering the worldwide burden of disease by TB, this study proposal aims to improve the current standard of care for LTBI treatment by assessing the effectiveness of an ultra-short antibiotic treatment in non-immunosuppressed patients. The one-month regimen of INH and RFT can reduce the length, costs, and adverse

effects of future LTBI treatments in comparison with current regimens. Moreover, this trial could provide valuable insights for future LTBI trials concerning activation rates of LTBI, heterogeneous patient populations and investigated drugs.

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Conflict of Interest

The authors followed the International Committee or Journal of Medical Journals Editors (ICMJE) form for disclosure of potential conflicts of interest. All listed authors concur with this manuscript submission; all authors have approved the final version. Also, the authors have no financial or personal conflicts of interest related to this research subject.

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