A Prospective, Randomized Controlled Study for the Efficacy and Safety of the Substitution of Pyrazinamide and Ethambutol With Moxifloxacin During the Intensive Phase of Treatment of Pulmonary Tuberculosis

Yuqi Shang
Fifth Affiliated Hospital of Sun Yat-sen University
Xi Liu
Fifth Affiliated Hospital of Sun Yat-sen University
Yuanli Chen
Fifth Affiliated Hospital of Sun Yat-sen University
Xiaoqing Luo
Fifth Affiliated Hospital of Sun Yat-sen University
Hongqiong Zhu
Fifth Affiliated Hospital of Sun Yat-sen University
Jinyu Xia
Fifth Affiliated Hospital of Sun Yat-sen University
Li Ding (dingli@mail.sysu.edu.cn)
Fifth Affiliated Hospital of Sun Yat-sen University

Research Article

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Abstract

Background: Moxifloxacin (MFX, M) is currently a second-line antituberculosis drug as initial therapy of pulmonary tuberculosis and one of the main anti-TB drugs in drug-resistant TB, which can kill both intracellular and extracellular Mycobacterium tuberculosis. We started a trial to study the efficacy and safety of the substitution of pyrazinamide and ethambutol with moxifloxacin during the intensive phase of treatment of newly diagnosed susceptive pulmonary tuberculosis.

Methods/design: This is a prospective, open, randomized, parallel-controlled, single-center clinical study. The study consists of three phases: a screening period, a treatment period of 6 (or 7) months, and a follow-up period of 1 year. Patients selected for the study will be allocated to the trial group or the control group randomly. The control group will be given six months of a standard regimen(2HRZE/4HR). The trial group will be given a total of six months of treatment with substitution of pyrazinamide and ethambutol with moxifloxacin during the intensive phase(2HRM/4HR). The primary outcome is the rate of adverse outcomes within one year of completion of therapy. The Secondary outcomes include the rate of treatment success at the 2nd, 3rd, 5th and 6th months, the rate of sputum Mtb(Mycobacterium tuberculosis) negative conversion at the 2nd, 3rd, 5th and 6th months, the time of sputum Mtb negative conversion at the 2nd, 3rd, 5th and 6th months, and the number of patients with adverse events within one year of completion of therapy. Comparisons will be performed using two-sided tests with a statistical significance level of 5%.

Discussion: This trial will reveal the effectiveness and safety of 2months of use of moxifloxacin instead of pyrazinamide and ethambutol during the intensive phase of treatment for newly diagnosed susceptive pulmonary tuberculosis. If the new regimen including isoniazid, rifampicin and moxifloxacin during the intensive phase of treatment (2HRM/4HR) is no less effective and safe than the standard regimen(2HRZE/4HR), it could be a new alternative treatment for newly diagnosed susceptive pulmonary tuberculosis in the future.

Trial registration: ClinicalTrials.gov, NCT04187469. Registered on 5 December 2019.

Introduction

Background

Tuberculosis (TB) is one of the ten most deadly diseases in the world, ranking first among infectious diseases. The number of tuberculosis patients in China ranks third in the world[1].

The most severe problems in the treatment of tuberculosis[2 3] are: (1) the current standard treatment plan has a long course and obvious side effects, reduces patients' compliance which may cause irregular medication or interrupted treatment, and drug resistance[4 5]; (2) the incidence of drug-resistant tuberculosis has been increasing due to non-standard treatment and other factors. An optimized existing anti-TB plan could help improve the current situation.

The current standard anti-tuberculosis regimen for newly diagnosed susceptive tuberculosis consists of two phases: the intensive phase and the consolidation phase. Isoniazid (INH, H), rifampicin (RFP, R), pyrazinamide (PZA, Z) and ethambutol (EMB, E) are used in the intensive phase, combined treatment for 2 months. And the consolidation phase is 4 months of the HR dual regimen, which is 2HRZE/4HR[6].

Moxifloxacin (MFX, M) is currently a second-line antituberculosis drug and can kill both intracellular and extracellular Mycobacterium tuberculosis[7]. Compared with two other second-line antituberculosis quinolone drugs –levofloxacin and gatifloxacin, moxifloxacin has a stronger early bactericidal activity[8].

Adding moxifloxacin or replacing one drug in the standard regimen with moxifloxacin, has resulted in increasing the negative conversion rate of sputum bacteria, reducing the recurrence rate, without causing additional adverse reactions[9-11]. However, the 4-month short-range anti-TB program containing moxifloxacin did not show non-inferiority compared to the standard 6-month anti-TB program[12-14].

The incidence of adverse reactions reached about 50% in the intensive phase of standard antituberculosis treatment, and the incidence of adverse reactions in each month of the consolidation phase was less than 5%[15].

Both INH and RFP can act on Mycobacterium tuberculosis in different periods, but PZA has no effect on tuberculosis bacteria outside the cell and EMB is effective only on fast-growing bacteria outside the cell[16]. Because of the strong anti-tuberculosis ability (inside and outside the cell) and the lower adverse reactions of moxifloxacin[17], it is an ideal alternative to the drugs PZA and EMB in the intensive phase.

This study will compare the short-term efficacy and safety, the recurrence rate after discontinuation, the impact on patients' compliance of the HRM triple-strengthening regimen with the standard HRZE quadruple-strengthening regimen.

Methods/design

Setting

This randomized controlled trial is to be conducted at the Fifth Affiliated Hospital of Sun Yat-sen University. The hospital is located in Zhuhai, China. The flow chart of the research process is shown in Figure 1.

Design

This is a prospective, open, randomized, parallel-controlled, single-center clinical study with two arms. Eligible patients are first screened by safety laboratory testing. Patients with the newly diagnosed TB are randomized to the following two arms at a 1:1 ratio:

1. Arm 1 (Control arm): Standard 2HRZE/4HR treatment[18] for newly diagnosed TB uses isoniazid (300mg/day, 6 months), rifampicin (≤ 50kg 450mg/day or > 50kg 600mg/day, 6 months), pyrazinamide (1500mg/day, 2 months), and ethambutol (≤ 50kg and the elderly 750mg/day or > 50kg 1000mg/day, 2 months).
2. Arm 2 (Investigation arm): 2HRM/4HR treatment using isoniazid (300mg/day, 6 months), rifampicin(≤ 50kg 450mg/day or > 50kg 600mg/day, 6 months), and moxifloxacin is used (400 mg/day, 2 months).

The schedule of treatments and data collection (also known as Clinical Research Flowchart) is shown in Table 1. Researchers evaluate treatment adherence during each visit. If a scheduled visit is delayed or cancelled, the research team will contact participants right now. No treatment or intervention is prohibited for the participants, and any ancillary and/or post-trial care is determined by the duty physician.

Outcomes

The primary outcome is the rate of adverse outcomes within one year of completion of therapy. The Secondary outcomes include the rate of treatment success at the 2nd, 3rd, 5th and 6th months, the rate of sputum Mtb negative conversion at the 2nd, 3rd, 5th and 6th months, the time of sputum Mtb negative conversion at the 2nd, 3rd, 5th and 6th months, and the number of patients with adverse events within one year of completion of therapy.

Definitions

Sputum Mtb negative conversion and Adverse outcomes

We define sputum Mtb negative conversion as two negative-culture results at different visits without an intervening positive result, or no sputum could be tested after once negative-culture.

Adverse outcomes is a sum of treatment failure and relapse. We define treatment failure as a patient whose sputum smear or culture is positive at 5 months or later during treatment. Relapse is patients with successful treatment show one of the following conditions at any time point during the observation period of drug withdrawal: 1) Sputum or Bronchoalveolar lavage fluid(BALF) culture positive, 2) Sputum or BALF acid fast stain and/or Xpert positive with active PTB evidence in CT scan.

The time of sputum Mtb negative conversion is the first time of sputum Mtb negative conversion.

Treatment outcomes

We define treatment outcomes as follows[19]:

Cure: We define cure as a patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.

Treatment completed: We define treatment completed as a patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion.

Treatment success: We define treatment success as a sum of cured and completed treatment.

Eligibility criteria for participants

Participants with pulmonary TB satisfying the inclusion criteria are competitively enrolled by investigators in both outpatient and inpatient settings in the one participating hospital.

The inclusion criteria are as follows:

(1) Aged 18 years or over, and an individual who completely bear the ability of

civil actions; (2) Aged 18 years or over, and an individual who completely bear the ability of civil actions; (3) Pulmonary tuberculosis patients with bacteriological diagnosis.

Patients will be excluded if they have HIV/AIDS. Female patients of childbearing potential who are pregnant, or breastfeeding, or unwilling to avoid pregnancy will also be excluded. Additionally, any of the following factors will lead to exclusion:

(1) Suffering from tuberculous pleurisy; (2) Patients with extrapulmonary tuberculosis; (3) Renal insufficiency patients with creatinine clearance rate <30 ml/min; (4) Abnormal liver function (ALT and/or AST and/or TBIL greater than 2 times the upper limit of normal) or decompensated cirrhosis; (5) HIV-Ab positive;

(6) Psychiatric patients, or have a previous history of mental illness, or recently have obvious anxiety or depression and other mental abnormalities; (7) Patients receiving immunosuppressive therapy; (8) Pregnant or breast feeding; (9) Diabetes; (10) X-pert MTB/RIF test of sputum or alveolar lavage fluid showed that Mycobacterium tuberculosis was rifampin resistant; (11) Moxifloxacin was used within 14 days before entering the group; (12) Anti-tuberculosis treatment has been started and drugs are being taken before entering the group; (13) The QT interval extension > 480 ms; (14) Combined with serious cardiovascular, liver, kidney, nervous system, blood system and other diseases, as well as tumor diseases; (15) Pulmonary lesions are widespread with respiratory insufficiency; (16) Any other circumstances in which the anti-tuberculosis scheme of the test group or the control group cannot be selected for treatment.

Randomization

Grouping is carried out using a permuted-block randomization method. Before the experiment, a statistical expert uses SAS software to set the length of the block to be 8, the number of blocks to be 36, a 1: 1 ratio between the test group and the control group, to generate 288 random numbers and corresponding grouping information. According to the haphazard allocation table in advance, the

statistical expert gives random numbers (1-288) in ascending order. Each random number and grouping information corresponds to an envelope. The envelope is sealed and given to the researchers responsible for screening. Qualified subjects are selected, and the envelopes are received in the order of enrollment. After the envelopes are opened, the random number and grouping information is taken out, so that the subjects will be randomly assigned to the experimental group or the control group, and the corresponding treatment and observation were performed. Each subject's random number is unique and is the same throughout the trial.

Justification of sample size

The hypothesis of this study is that the use of moxifloxacin instead of pyrazinamide and ethambutol will not increase the rate of adverse outcomes within one year of completion of therapy.

Hypothesis for sample size calculation

H_0(null hypothesis): $P_T - P_C \geq \triangle$ (new regimen adverse outcomes rate within one year of completion of therapy is higher than that of the conventional treatment).

H_1(alternative hypothesis): $P_T - P_C < \triangle$ (new regimen adverse outcomes rate within one year of completion of therapy is not higher than that of conventional treatment).

Assumptions

In the control group, the proportion of adverse outcomes within one year of

completion of therapy was about 10%[14]. The margin of the non-inferiority of the test group and the control group may be 6%[14]. based on an α = 0.05 level of significance, a power of 85%, and the ratio of the test group to the control group was 1: 1. It is found that the number of statistical cases is not less than 119 in each group. Taking into account factors such as drop-out, an increase of about 20% of the subjects, that is, 143 subjects in the test group and 143 subjects in the control group were required, for a total of 286 subjects.

Statistical analysis

The results of this trial for efficacy outcomes will be analyzed based on both intention-to-treat (ITT) and per protocol (PP) approaches with a primary consideration for ITT results. A PP analysis will be performed secondarily. A safety analysis will be performed based on the safety group.

The ITT group will include participants who are randomized after satisfying eligibility criteria and receive one study drug at least one time and have a post-dose evaluation data. The PP group will include participants who satisfy the following conditions among the ITT group: (1) those who completed all planned visits, (2) those who did not use and receive drugs or treatments that may affect the evaluation

of efficacy during the trial. The safety analysis group will include participants who receive study drugs at least once and have a post-dose safety evaluation data.

Efficacy outcomes

Comparisons will be performed using two-sided tests with a statistical significance level of 5% unless stated otherwise.

Analysis of primary outcomes

For the primary outcome of this trial, the rate of adverse outcomes within one year of completion of therapy will be estimated as the proportion with a 95% confidence interval for each treatment group. The difference between the control arm and experimental arm will subsequently be determined using the chi-square test or Fisher's exact test.

Analysis of secondary outcomes

The analysis of secondary outcomes will be described as explorative outcomes. The rate of sputum Mtb negative conversion among the two groups will be compared using the chi-square test or Fisher's exact test. The time of sputum Mtb negative conversion will be calculated in each group and compared using a log-rank test. The rate of treatment success, and the number of patients with adverse events will be compared among the two groups using the chi-square test or Fisher's exact test.

Safety assessment

All AEs and serious AEs (SAEs) according to the Common Terminology Criteria for Adverse Events (CTCAE) will be collected and documented, regardless of severity, seriousness, or relationship to the study drug. We will summarize all AEs and SAEs, AE frequency and percentage, and 95% confidence intervals. We will compare the occurrence rate of AEs in relationship to the study drug and severity of the two arms using the chi-square test or Fisher's exact test.

Stratified analysis

Primary and secondary outcomes will be analyzed separately in participants with sputum smear-positive and smear-negative pulmonary TB.

Data collection and management

This study will use a paper version of the case report form(CRF) and establish a clinical research database to record all the information in the CRF. Use the software Epidata3.1 for double entry and proofreading of data, as well as manual verification and system verification.

During the study, medical personnel not participating in this study will monitor this trial. Monitors will visit database to monitor all aspects of the study including adherence to the protocol and good clinical

practice, protection of participants, and data accuracy of the study.

Supervision of the trial

Office of Clinical Research Center and the Medical Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University form the data and safety monitoring board. Based on data review during the trial conduct, the board may provide recommendations such as protocol amendment, continuation, or stopping of the trial.

Confidentiality

We will collect the participants' personal information only when necessary to evaluate efficacy, safety, and tolerability of the study drugs. Such information will be collected and processed taking precautions for compliance with laws on privacy protection and guaranteeing of confidentiality. Paper files containing participants' data (including personally identifiable information and copies of signed consent forms) will be securely stored in a locked office on sites in locked filing cabinets. Digital files containing participants' data will be stored in password-protected files on university-maintained servers. Access to study files will be restricted to authorized personnel only.

The items in the present study protocol comply with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (see the SPIRIT

Checklist and figure in Additional file).

Clinical trial registration

The trial was registered under the registration number NCT04187469 (https://clinicaltrials.gov/ct2/show/NCT04187469?term=NCT04187469&draw=2&rank=1) on 5 December 2019. On December 26, 2018, this research was approved by the Medical Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University, ZDWY[2018] Lunzi No. (K54-1).

Discussion

Develop a new anti-TB treatment regimen could improve not only treatment outcomes of patients but also TB control in the world. Based on higher culture conversion rates in TB patients treated with regimens, containing moxifloxacin[10 11], we are conducting a research using moxifloxacin instead of pyrazinamide and ethambutol for newly diagnosed pulmonary TB.

If a new regimen including moxifloxacin shows lower adverse outcomes rate and number of patients with adverse events, higher treatment success rate and sputum Mtb negative conversion rate, a shorter time of sputum Mtb negative conversion, it will be a big step forward in anti-TB treatment.

The potential clinical value of the HRM triple-strengthening regimen instead of the standard quadruple-strengthening regimen is evaluated, and a basis for developing a new optimized PTB treatment plan is provided. This study is an improvement and innovation of the existing standard quadruple strengthened anti-TB scheme, and has far-reaching clinical significance.

The results of this study will provide meaningful information and evidence for clinical practice and will help design a proven and reasonable RCT(Randomized Controlled Trial) soon.

Limitations

Randomized controlled studies still have some design limitations. First, the sample size is relatively small. We will not be able to estimate the possible relapse of PTB after treatment. Second, the pathophysiology of PTB has not been elucidated. Finally, whether the follow-up period in this study is relatively short. In light of these limitations, we will develop a more reasonable treatment cycle and follow-up period to explore the effectiveness and safety of the triple strengthening scheme. Additionally, as the project undertaker is a designated hospital for COVID-19, the project that was originally scheduled to start in March 2020 had to be postponed due to the impact of the global COVID-19 epidemic.

Trial status The trial was registered under the registration number NCT04187469(https://clinicaltrials.gov/ct2/show/NCT04187469?term=NCT04187469&draw=2&rank=1) on 5 December 2019. On December 26, 2018, this research was approved by the Medical Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University, ZDWY[2018] Lunzi No. (K54-1). Unique Protocol ID: ZDWY.GRK.004. Protocol version date: July 11, 2019. The first participant was randomized on March 21, 2021, and recruitment is ongoing. It is estimated that the recruitment will be completed on October, 2023. The final results will be reported in 2025.

Abbreviations

TB: Tuberculosis; PTB: Pulmonary Tuberculosis; INH, H: Isoniazid; RFP, R: Rifampicin; PZA, Z: Pyrazinamide; EMB, E: Ethambutol; MFX, M: Moxifloxacin; Mtb: Mycobacterium tuberculosis; CT: Computed Tomography; HIV: Human Immunodeficiency Virus; BALF: Bronchoalveolar Lavage Fuid; PPD: Purified Protein Derivative; AIDS: Acquired Immune Deficiency Syndrome; Xpert: X-pert MTB/RIF; WHO: World Health Organization; ESR: Erythrocyte Sedimentation Rate; CRP: C-Reactive Protein. ECG: Electrocardiograph; T-SPOT: T-SPOT.TB; CRF: Case Report Form; DRQ: Data Rating Questionnaire; AE: Adverse Event; SAE: Serious Adverse Event; FAS: Full Analysis Set; ITT: Intention-to-treat; PPS: Per Protol Set; SS: Safety Set; SOP: Standard Operation Procedure; GCP: Good Clinical Practice; COVID-19: Corona Virus Disease 2019.

Declarations

Acknowledgements

Not applicable.

Authors' contributions

LD and JX, Professors carried out the design of the study. YS and XL, participated in the study design and drafted the manuscript. YC, XL and HZ follow the research and help to collect data. All authors read and approved the final manuscript.

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This study was not funded.

Availability of data and materials

The datasets used or analyzed in the current study are available from the corresponding authors on reasonable request.

Ethics approval and consent to participate

This study was reviewed and approved by the Medical Ethics Committee of the Fifth Affiliated Hospital of Sun Yat-sen University in Zhuhai on December 26, 2018, with file number ZDWY[2018] Lunzi No. (K54-1). This study is designed in accordance with the principles of the Declaration of Helsinki. All participants will provide written informed consent before enrolment.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

Author details

[1]Department of Infectious Diseases, The Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, China

[2]Department of Nosocomial Infection Management, The Fifth Affiliated Hospital, Sun Yat-sen University, Zhuhai, China

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Tables

Due to technical limitations the Table is available as a download in the Supplementary Files.

Figures

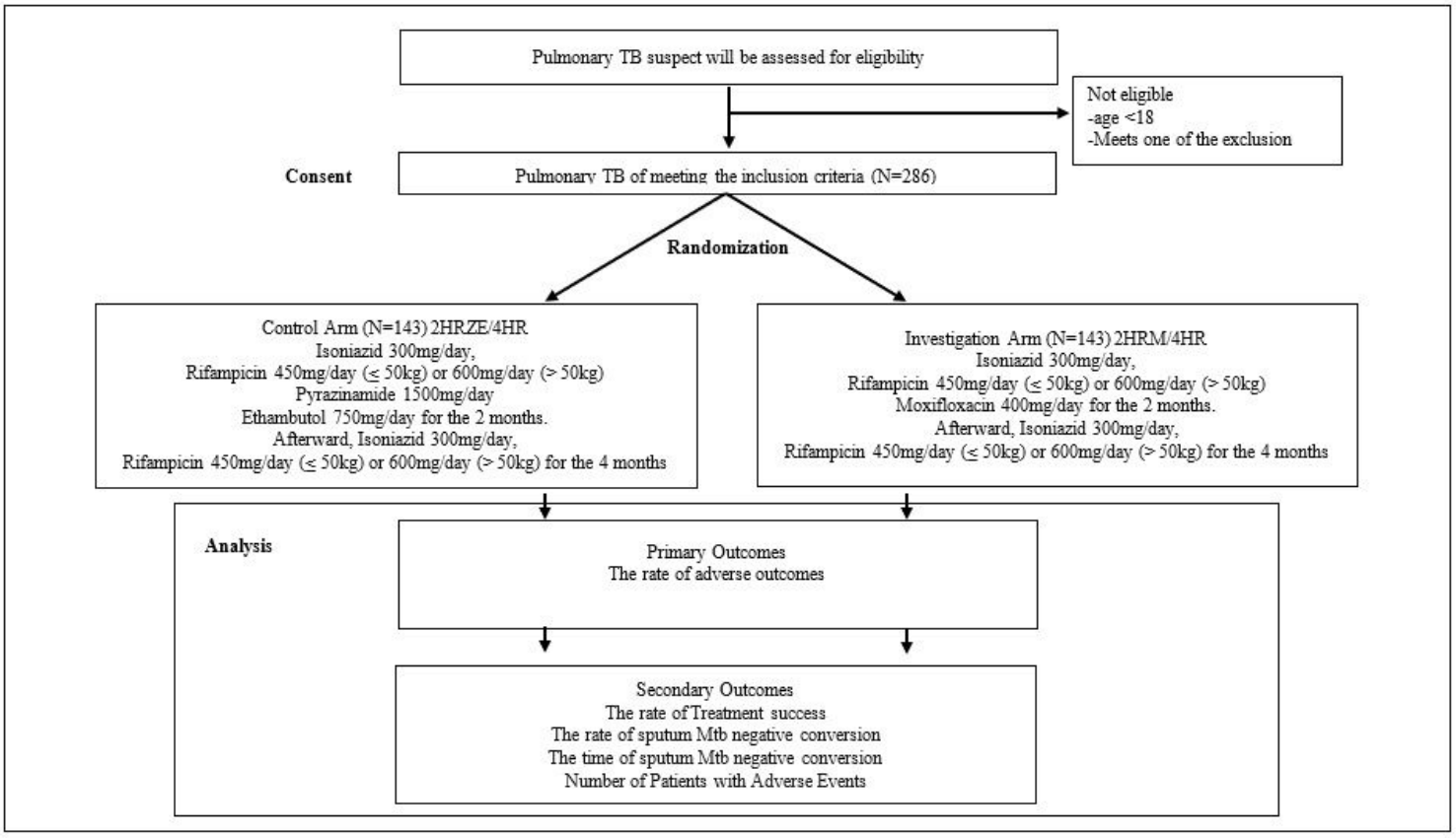

Figure 1

The flow chart of the research process

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table1.pdf
- Additionalfile1.SPIRIT2013Checklist.docx