Study Protocol

Six-month versus nine-month therapy for intestinal tuberculosis: a protocol for a randomized controlled study

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Background: The optimal duration of treatment for intestinal tuberculosis (TB), which remains a common disease worldwide, has not yet been established. The proposed randomized controlled study will aim to compare the efficacy of short-term six-month with nine-month anti-TB therapy for treating intestinal TB.

Methods: This multicenter, open-label, double-blinded, randomized controlled trial conducted in the Affiliated Hangzhou Chest Hospital of Zhejiang University will include a total of 80 patients. Patients who meet the inclusion criteria will be randomly assigned to either the six-month (n=40) or nine-month (n=40) treatment group. The primary outcome will be complete response, which is defined as endoscopy displaying active lesion healing at the end of treatment. Participants will be scheduled for follow-up visits once a month in the first three months, then once every three months until the end of the treatment. The last follow-up will be one year after the treatment. Recurrence will be assessed one year after the end of treatment, which is defined as endoscopy displaying recurrent lesions after complete response.

Discussion: In addition to the reports of tuberculous lymphadenitis and spinal TB, there are few appropriate randomized trials for the treatment of extrapulmonary TB with appropriate clinical endpoints. We believe that the proposed randomized controlled trial will provide further data on the efficacy of short-term six-month anti-TB therapy in intestinal TB patients.

Trial Registration: This trial will be registered on ClinicalTrial.gov.

Keywords: Intestinal tuberculosis (intestinal TB); short-term therapy; randomized controlled trial; complete response

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Introduction

Tuberculosis (TB) can occur in almost any organ or tissue of the body, and the range of clinical diseases is very wide. This disease has been successfully controlled since the introduction of effective anti-TB treatments and the improvement in people's living standards. However, in recent decades, there has been a trend towards resurgence of TB worldwide, and the global infection rate was estimated to be more than 30% according to the tuberculin surveys in 1997. The main reasons include the prevalence of human immunodeficiency virus (HIV) infection in some developing and developed countries. Moreover, the appearance of multidrug-resistant *Mycobacterium tuberculosis* has posed an increasing challenge to the successful control of TB in several parts of the world (1-3). TB is still a major problem in Africa and Asia, and continues to induce considerable morbidity and mortality in these regions (4). Extrapulmonary TB is becoming more and more common: the incidence of extrapulmonary organ infection was estimated to be between 15% and 20% in patients who are not infected by HIV, however, in those who are infected with TB and HIV concurrently, the incidence was reported to be between 50% and 70% (3,5,6).

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Among the extrapulmonary TB infections, intestinal TB is one of the most common diseases. The intestinal organs that are mainly involved include the distal ileum and cecum, followed by the jejunum, ileum, colon, and rectum (5,7,8). Intestinal TB has been prevalent and has been a major health problem in developing countries. Combination chemotherapy with isoniazid, rifampicin, pyrazinamide, and ethambutol for six months has been a common and effective therapy for treating pulmonary TB. Adding pyrazinamide to this therapy containing isoniazid and rifampicin can shorten the treatment duration from nine months to six months (9). Although studies that have investigated extrapulmonary TB therapies are limited, there are reports that the basic principles of TB treatment can also be applied to extrapulmonary TB infections (5,10-12). However, due to the difficulties of assessing bacteriological diagnosis and treatment response, many doctors, especially those in developing countries, have been reluctant to use six-month treatment for extrapulmonary TB, such as intestinal TB.

Few randomized controlled studies investigating the optimal treatment duration of intestinal TB have been performed, except for several retrospective reviews (13,14). Park *et al.* initiated a similar trial in 2009, however, it is not of double-blind design (15). Therefore, we aim to conduct this randomized, double-blind, clinical trial to compare the effect of six-month versus nine-month therapy in intestinal TB patients. We present the following article in accordance with the SPIRIT reporting checklist (16) (available at https://dx.doi.org/10.21037/apm-21-1642).

Methods

Study design

This trial will be a multicenter, open-label, double-blinded, randomized controlled trial conducted in Zhejiang, China. Patients with a clear diagnosis of intestinal TB will be eligible for the trial, and intestinal TB can be definitely diagnosed if at least one of the following criteria is met: (I) endoscopic biopsy shows caseous granuloma; (II) the histological specimen identifies the acid-fast bacilli; (III) *Mycobacterium tuberculosis* is positive in biopsy specimens; (IV) typical colonoscopy results strongly suggest that intestinal TB is associated with active pulmonary TB, regardless of acid-fast bacilli smear or sputum mycobacterium culture. The exclusion criteria will include: (I) age less than 18 years or more than 80 years; (II) infected with other extrapulmonary TB but not intestinal TB; (III) received anti-TB chemotherapy in the past three years; and (IV) with concurrent chronic liver disease or immunosuppressive disorder. Patients who are pregnant will also be excluded in this trial for security reasons. The study design has been approved by the Review Board of the Affiliated Hangzhou Chest Hospital of Zhejiang University, and all the enrolled patients will be asked to give their informed consent.

Pre-treatment evaluation and follow-up

At the beginning of the trial, all patients will provide their medical and family history, then they will all receive a chest X-ray, blood counts, routine biochemical tests, and a complete physical examination. All patients will receive a colonoscopy both at the beginning of the trial and at the end of the anti-TB therapy. Patients will be scheduled for follow-up visits once a month in the first three months, then once every three months until the end of the treatment. The last follow-up will be one year after the treatment.

Interventions and control

The flow diagram of the proposed randomized controlled trial is showed in *Figure 1*. Patients with intestinal TB who meet the inclusion criteria will be randomly divided into two groups and treated with chemotherapy for either six months or nine months. A 1:1 simple randomization procedure will be used for the randomization based on a computer-generated randomization list. Only one external manager that is not involved in the trial will have the possession of the randomization list, and others including patients and care providers will all be blinded to the randomization. The six-month group of patients will receive the Z2H6R6E6 cocktail, which consists of rifampin, ethambutol, and isoniazid for six months, together with pyrazinamide for the first two months. Patients in the nine-month group will receive the Z2H9R9E9 combination, which is composed of rifampin, isoniazid, and ethambutol for nine months, together with pyrazinamide for the initial two months. Because of the high rate of primary drug resistance in South Korea (17), we will retain ethambutol for continued use. Isoniazid will be given at a dose of 300 mg/day for patients under 50 kg of body weight and 400 mg/day for those over 50 kg. Rifampin will be given at a dose of 450 mg/day for patients under 50 kg of body weight and 600 mg/day for those over 50 kg. The doses of ethambutol (15–20 mg/kg) and pyrazinamide (20–30 mg/kg) will be, respectively,

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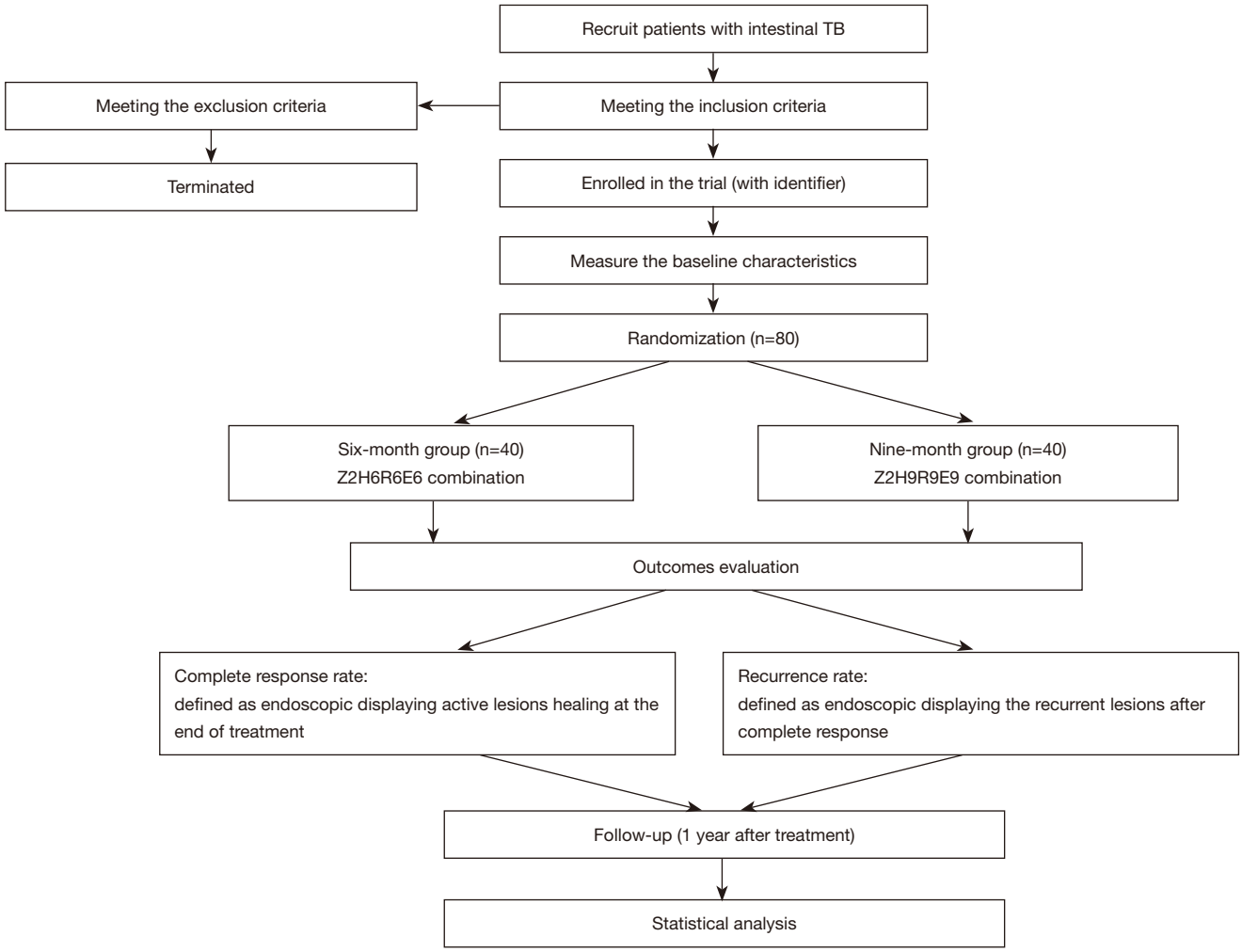

Figure 1 The flow diagram of the proposed randomized controlled trial. TB, tuberculosis; Z2H6R6E6, rifampin, ethambutol, and isoniazid for six months, together with pyrazinamide for the first two months; Z2H9R9E9, rifampin, isoniazid, and ethambutol for nine months, together with pyrazinamide for the initial two months.

1,000 mg/day and 1,250 mg/day for those under 50 kg of body weight, and 1,200 mg/day and 1,500 mg/day for those over 50 kg. After the initial two months, the dose of ethambutol will be reduced to 800 mg/day for all participants. Corticosteroids will not be used for any participants, while surgery will mainly be used to treat intestinal obstruction, perforation, fistula, and other complications (18).

Discontinuation

Discontinuation criteria will include serious adverse events, complications, and failure to continue the trial. Patients who cannot carry out the corresponding treatment or participate in the outcome assessment due to personal reasons will also be terminated. For these patients, the reason for discontinuation will be recorded clearly, and the outcomes will be recorded and evaluated in detail. Serious adverse events will be reported to the ethics committee immediately. No interim analysis will be performed in the proposed study.

Outcomes

The data of the two groups at diagnosis, treatment end, and one year after the treatment end will be compared to evaluate the improvement in abdominal symptoms and the rate of complete healing of active lesions in endoscopic recording.

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Complete response will be defined as endoscopy displaying active lesion healing at the end of treatment. Recurrence will be defined as endoscopy displaying recurrent lesions after complete response. Since most recurrences occur within the first six to twelve months after discontinuation of treatment (9,19), we will not assess the disease status until one year after the end of treatment.

Sample size

A total of 80 patients (40 in each group) will be needed to realize the statistical power if the true success rate in the nine-month group is set as 95%, and the possibility that the success rate in the six-month group is at least 5% less than that of the nine-month group (the noninferiority of the six-month group hypothesis; one-sided $P<0.05$).

Data collection and management

Baseline characteristics of the enrolled patients will be collected by two authors independently. Data collected will include age, gender, weight, previous history of intestinal TB, and corresponding treatment received. Double data entry will be used to promote data quality. All the data will be reviewed by the data monitoring committee, which is composed of five professional experts who are blinded to the trial process, so as to increase the accuracy of our data.

Statistical analysis

All outcomes will be compared on the basis of the intention-to-treat principle. The Wilcoxon rank sum test will be used to compare continuous variables between groups, while the chi-squared test or Fisher's exact test will be used for categorical variables, as appropriate. Subgroup analyses will be performed based on different age groups and gender. All P values will be two-sided, with $P<0.05$ considered as statistically significant. Analyses will be performed using SPSS Software (version 21.0, SPSS Inc., Chicago, IL).

Ethics

Prior to the start of this study, we obtained approval of this protocol from the Review Board of the Affiliated Hangzhou Chest Hospital of Zhejiang University. Before the clinical trial, all participants will provide written informed consent to participate in the study. A clinician in our hospital who is blinded to the trial process will collect the written informed consent and the information collected will be strictly confidential. Any changes to the protocol will be reported to the Review Board immediately. All procedures performed in this study involving human participants will be in accordance with the Declaration of Helsinki (as revised in 2013).

Discussion

Based on the data of *in vitro* and animal experiments, clinicians have made efforts to shorten the treatment duration of pulmonary TB (20). In these studies, the combination of drugs that are effective in killing propagules (isoniazid and rifampicin) and drugs that attack intracellular organisms (pyrazinamide) was used to improve the overall efficacy of chemotherapy and allow the total duration of treatment to be shortened to six months. In our opinion, these data seem to be applicable to the treatment of extrapulmonary TB.

The treatment of intestinal tuberculosis depends on regular anti tuberculosis drug therapy and the improvement of life style. Our study aims to investigate whether six-month therapy is effective in treating intestinal TB. Up to now, there is growing data which suggests that therapies with isoniazid and rifampin are indeed effective for this disease. Therefore, a six-month duration of treatment is recommended for TB in any part of the body except the meninges, and in some cases, the bones, where nine- to twelve-month treatment may be applied instead. However, in addition to the reports of tuberculous lymphadenitis (21,22) and spinal TB (23-25), there are few appropriate randomized trials for the treatment of extrapulmonary TB with appropriate clinical endpoints. We believe that our trial will provide important data comparing the efficacy of short-term six-month therapy with longer-term nine-month therapy. The above steps will be implemented strictly to ensure the reliability of our results.

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Footnote

Reporting Checklist: The authors have completed the SPIRIT reporting checklist. Available at https://dx.doi.org/10.21037/apm-21-1642

Conflicts of Interest: All authors have completed the ICMJE

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uniform disclosure form (available at https://dx.doi.org/10.21037/apm-21-1642). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures performed in this study involving human participants will be in accordance with the Declaration of Helsinki (as revised in 2013). The study design has been approved by the Review Board of the Affiliated Hangzhou Chest Hospital of Zhejiang University, and all the enrolled patients will be asked to give their informed consent.

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