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Daily versus three-times-weekly azithromycin in Chinese patients with non-cystic fibrosis bronchiectasis: protocol for a prospective, open-label and randomised controlled trial

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ABSTRACT

Introduction Non-cystic fibrosis bronchiectasis (NCFB) brought a heavy healthcare burden worldwide. Macrolide maintenance therapy was proved to be helpful in reducing exacerbation of NCFB. However, the optimal dosing regimens of macrolides have not been determined, and its efficacy in Chinese NCFB population has not been validated. This protocol describes a head-to-head clinical trial designed to compare the efficacy of two dosing regimens of azithromycin in Chinese NCFB population.

Methods and analysis This prospective, open-label and randomised controlled trial will be conducted in the First People's Hospital of Jiashan, China. Eligible patients with high-resolution CT defined NCFB will be randomly divided into three groups, which will receive either 250 mg daily azithromycin, or 500 mg three-times-weekly azithromycin or no treatment for 6 months. They will be followed up for another 6 months without treatment. The primary outcome is the mean rate of protocol-defined pulmonary exacerbation at 6 months.

Ethics and dissemination Ethical approval was obtained from the First People's Hospital of Jiashan Ethics Committee. The findings will be disseminated in peer-reviewed publications.

Trial registration number ChiCTR2100052906.

INTRODUCTION

Bronchiectasis is a condition characterised by an airway inflammatory response to bacterial pathogens.[1 2] Bronchiectasis is usually classified as either being caused by cystic fibrosis or non-cystic fibrosis. Non-cystic fibrosis bronchiectasis (NCFB) is more prevalent worldwide in part due to greater availability of chest CT imaging.[3] Despite of better control of airway infections, the prevalence of NCFB is still on rise. From 2000 to 2007, the prevalence of NCFB in America has increased with an annual percentage of 8.74%.[4] In addition, acute exacerbations of NCFB, which are characterised by increases in symptoms requiring

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Strengths and limitations of this study

⇒ This study is a prospective, head-to-head, randomised trial, which is the best study design to address the research question.
⇒ This study use a novel consensus definition of bronchiectasis exacerbation, which increase the validity of the results.
⇒ The lack of blinding of interventions is a limitation of the study design.
⇒ Another limitation of this trial is that it does not have a multicentre design.

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antibiotic treatment, result in the destruction of airways, reduced pulmonary function, deteriorated quality of life and increased mortality.[5–7] Therefore, NCFB has brought a heavy healthcare burden worldwide.[4 8–10]

Since NCFB is not reversible, its management is mainly to prevent exacerbation and improve quality of life.[2 11–13] The use of macrolides to prevent exacerbation has been describe by many published studies.[14–16] Several influential randomised controlled trials (RCTs) have shown a clear benefit in terms of reducing the exacerbation by macrolides.[17–19] The EMBRACE study revealed that azithromycin reduced exacerbations by 62% in the 6-month treatment period, and continued to reduce exacerbations by 42% for 6 months following the treatment period.[19] The BAT study showed that azithromycin not only reduced exacerbations by 34%, but also significantly increased forced expiratory volume in 1 s and improved quality of life.[17] The BLESS study confirmed that use of erythromycin brought a 43% reduction of exacerbations in the 12-month treatment period.[18] Moreover several systematic reviews and meta-analysis

were in agreement with the benefit of macrolides maintenance therapy.[6 15 20] Therefore, macrolides maintenance therapy have been advised by various guidelines and consensus.[21–23]

There are still uncertainties regarding macrolides maintenance therapy in prevention of NCFB exacerbation.[20 24 25] In 2016, The European Multicentre Bronchiectasis Audit and Research Collaboration Clinical Research Collaboration identified dozens of research priorities in NCFB, of which several priorities were associated with antibiotic maintenance treatment.[26] One of these priorities was the optimal choice of antibiotic maintenance treatment in preventing exacerbation. So far macrolides have been the most studied antibiotic for preventing exacerbation, but the optimal dosing regimens of macrolides remain unknown.[6 11 27] The published studies had examined multiple dosing regimens with different macrolides antibiotics, dosage, frequency and duration of medication.[6 15 20] Although the studies had reached an agreement that macrolides maintenance therapy had advantages over placebo in preventing exacerbation, the optimal regimens have not been determined yet. Because comparison across studies is problematic and inconvincible, head-to-head studies to clarify the optimal regimens are warranted. But so far head-to-head studies in this field is still absent.

Available studies about macrolides maintenance therapy were conducted mostly in Caucasian population. So the evidence of macrolides maintenance therapy in Chinese population is still lacking. Racial and ethnic factors, such as genetics, body size and fat distribution, contribute to differences in pharmacokinetics of drugs. Pharmacokinetic differences between racial and ethnic groups had been reported for macrolides, which may influence its efficacy in NCFB.[28] Yu *et al*[29] found that for a single oral dose of erythromycin, Koreans had a 65% higher AUC (area under curve) from time zero to infinity (AUC_∞) than Caucasians. Interethnic pharmacokinetic differences of clarithromycin and azithromycin between non-Caucasians and Caucasians have been described as well.[28] So the efficacy of macrolides maintenance therapy in Chinese NCFB population is needed to validated by further research.

Thus, we set out to compare two commonly used dosing regimens (250 mg daily vs 500 mg three times weekly) of azithromycin in a head-to-head trial in Chinese NCFB population. Azithromycin was chosen for several reasons. First, azithromycin was widely used for a variety of indications and had a better side effect profile. Second, existing evidence were derived mainly from studies of azithromycin, rather than other macrolides.[16 17 19] At last, azithromycin was found to be more efficient than roxithromycin and erythromycin in preventing exacerbation of NCFB in systematic review.[15] Regarding regimen, those two dosing regimens of azithromycin had been tested in BAT and EMBRACE study, respectively, and both reduced exacerbations significantly.[17 18] But there is no head-to-head comparison of the two dosing regimens.

METHODS AND ANALYSIS
Study design and setting
This prospective, open-label and RCT will be conducted in the First People's Hospital of Jiashan, China. Patient enrolment will start on 1 January 2022.

Patients and public involvement
Patients or the public will not be involved in the design, or conduct, or reporting, or dissemination plans of our research.

Recruitment
The schedule of enrolment, interventions and assessments for this trial is described in table 1. Patients with stable NCFB will be recruited from those referred to the Department of Respiratory and Critical Care Medicine. Eligible patients will be invited to participate and asked to provide written informed consent before any study procedure occurs.

Inclusion criteria
1. Patients are 18 years or older.
2. Patients have a diagnosis of bronchiectasis defined by high-resolution CT.
3. Patients had at least one documented exacerbation requiring systemic antibiotic treatment in the preceding year.

Exclusion criteria
1. A history of cystic fibrosis.
2. A positive culture of non-tuberculous mycobacteria in the past 2 years.
3. Allergic bronchopulmonary aspergillosis.
4. Pregnant or lactating women, or fertile women with a pregnancy plan.
5. Elevated transaminase levels (aspartate aminotransferase and alanine aminotransferase levels equal to or greater than the upper limit of normal).
6. Unstable arrhythmia, especially prolonged QTc.
7. Macrolide treatment for more than 3 months in the past 6 months.

Withdraw criteria
1. Intolerable adverse effects.
2. The patient wishes to withdraw before the end of the trial.
3. The patient is not suitable for further trial inclusion due to other accidents.
4. Poor adhere to the follow-up schedule.

Baseline assessment
Patients will be assessed immediately after confirmation that they have met the initial eligibility criteria and provided informed consent. The baseline assessment will include the patient's age, height, weight, medical history, full blood count, routine blood chemistry test, C reactive protein (CRP), ECG, St George's Respiratory Questionnaire (SGRQ), Modified British medical Research

Table 1 Schedule of enrolment, interventions and assessments

	Study period						
	Enrolment	Allocation	Postallocation			No-intervention follow-up	
Time point	**0**	**0**	**weeks 4**	**weeks 13**	**weeks 26**	**weeks 39**	**weeks 52**
Enrolment :							
Eligibility screen	○						
Informed consent	○						
Allocation		○					
Interventions:							
Daily azithromycin			───────────────				
Three-times-weekly azithromycin			───────────────				
No treatment			───────────────				
Assessments:							
Full blood count	○				○		○
Routine blood chemistry	○				○		○
CRP	○				○		○
SGRQ	○		○	○	○	○	○
mMRC	○		○	○	○	○	○
CAT	○		○	○	○	○	○
ECG	○		○				
Adverse events			○	○	○		

CAT, chronic obstructive pulmonary disease assessment test; CRP, C reactive protein; mMRC, Modified British medical Research Council; SGRQ, St George's Respiratory Questionnaire.

Council (mMRC) and chronic obstructive pulmonary disease assessment test (CAT).

Intervention
Patients were given either daily azithromycin (250 mg once per day), or three-times-weekly azithromycin (500 mg Monday, Wednesday and Friday every week) or no treatment for 6 months. They will be followed up for another 6 months without treatment. Clinic visits were scheduled at weeks 4, 13, 26, 39 and 52, and telephone calls were scheduled every 2 weeks between visits. At each clinic visit, data of SGRQ, mMRC CAT and adverse events were collected; at weeks 4 visit, ECG was also ordered. Adherence was assessed by pill counts. At weeks 26 and 52 visit, additional full blood count, routine blood chemistry test, spirometry and CRP were evaluated.

Primary outcome
The primary outcome is the mean rate of protocol-defined pulmonary exacerbation (PDPE) at 6 months, analysed by intention to treat (all randomised participants who contributed data). Criteria for PDPE were based on a consensus definition proposed by Hill *et al*.[30] A PDPE was considered to have occurred when a person with bronchiectasis with a deterioration in three or more of the following key symptoms for at least 48 hours: cough; sputum volume and/or consistency; sputum purulence; breathlessness and/or exercise tolerance; fatigue and/or malaise; haemoptysis and a clinician determines that

a change in bronchiectasis treatment is required. A designated pulmonary physician, who is blinded to treatment allocation, will decide whether to treat exacerbations with antibiotics.

Secondary outcomes
Secondary outcomes are time to first PDPE, rate of PDPE at 12 months, SGRQ score at 6 months, mMRC at 6 months, CAT at 6 months, CRP at 6 months and adverse events.

Sample size
This study examines the two following hypotheses. The first hypothesis was that daily azithromycin and three-times-weekly azithromycin would bring similar rate of exacerbation at 6 months. In EMBRACE study, three-times-weekly azithromycin reduced exacerbations by 62% at 6 months, so non-inferiority margin was set at 31%. We estimated that about 38 patients in each group would need to be enrolled for the study to have a power of 80% to assess the non-inferiority in the 6-month treatment period between the two groups, assuming a two-sided α level of 0·05 and a 20% drop-out rate. The second hypothesis was that daily azithromycin would cause reduction of exacerbations compared with placebo. And according to EMBRACE study, azithromycin treatment would reduce the number of exacerbations by 62%. We calculated that a sample size of 41 participants in each group was required to detect this reduction with a one-sided α level of 0·025

and a power of 80%, assuming a 20% drop-out rate. To meet both hypotheses, 41 participants will be needed in each group, that is, a total of 123 patients for 3 groups.

Randomisation and allocation

After eligibility assessment, all patients will be informed about the nature and purpose of the study and will only be included after agreeing with the study and signing the informed consent form, which will be obtained by the pulmonary physicians. Randomisation will be requested by the physicians responsible for recruitment. A randomisation tool (www.randomization.com) will be used for block randomisation.[31] Randomisation sequence was created with a 1:1:1 allocation using random block sizes of 6 and 9 by an independent statistician. For concealment, 123 consecutive numbers will be placed in 123 opaque-sealed envelopes. The subjects will be assigned to a group in accordance with the distribution plan determined by the number contained in the random envelope that they receive. The person who produces and stores the randomly assigned sequence and the pulmonary physician who assesses the eligibility of the subjects will not be the same person.

Blinding

Due to the significant difference between interventions, neither the patients nor the treatment providers can be blinded to treatment arms. The assessment of primary and secondary outcomes will not be blinded. The pulmonary physician, who decide whether to treat exacerbations with antibiotics, will be blinded to the treatment arms. In addition, the statistician conducting the analyses will also be blinded to the treatment arms until the analysis have been completed.

Data management

All data will be collected and managed in Clinical Trial Management Public Platform ResMan. All data will be entered by the study team, and data accuracy will be verified by the study principal investigator (PI). Only study team members will have access to protected health information. All study-related information will be stored securely at the study site. All computers will be password protected per hospital policy. All physical participant information will be stored in locked file cabinets in areas with limited access. We will ensure that the anonymity is maintained. Patients will not be identified by name in any reports on this study. The study PI will have access to the final study dataset.

Data monitoring committee

Since this trial has a short duration and azithromycin has a good side effect profile, there is no need for a data monitoring committee.

Statistical analysis

All analyses will be conducted by a statistician who is blinded to the treatment arms. Primary outcome analysis will be performed by intention to treat, but a per-protocol analysis will also be conducted. Comparisons between three groups will be analysed via one-way analysis of variance (normally distributed data) or Kruskal-Wallis statistic (nonparametric data). The χ^2 analysis will be used for categorical data. All statistical analyses were conducted using SPSS V.20; statistical significance was denoted by $p < 0.05$.

Adverse events

Safety assessments will include reports of adverse events, serious adverse events, clinical laboratory tests and physical examinations, as well as the follow-up assessments.

Modification of the protocol

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures or significant administrative aspects will require a formal amendment to the protocol. Such amendment will be approved by the ethics committee prior to implementation and notified to the health authorities in accordance with local regulations.

ETHICS AND DISSEMINATION

Ethical approval was obtained from the First People's Hospital of Jiashan Ethics Committee. There are no interim analyses in this trial. However, the committee will audit trial conduct every other year to track any amendment or serious adverse events and have the right to terminate the trial. The results will be submitted for publication to an international, peer-reviewed journal, regardless of whether the results are positive or negative in relation to the study hypothesis.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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