FCRM.TB
Research on Tuberculosis

PROTOCOLE

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Country : Republic of Congo

Study type: Interventional, prospective, randomized, open label pilot study

Study phase and classification: Investigator Initiated Study

Full title of study and acronym

Assessment of immunomodulatory effects of Azithromycin in pulmonary tuberculosis patients

[AZT-TB]

Primary objective

The primary objective of this project is to evaluate the immunomodulatory effects of Azithromycin in pulmonary TB patients.

Hypothesis

I hypothesize that Azithromycin in conjunction with standard care can prevent the formation of persistent lung damage via its immunomodulatory effects.

Specific objectives

Specific Objective 1: Assess the effect of Azithromycin in addition to standard 2HRZE/4HR treatment on sputum microbiology;

Specific Objective 2: Investigate the immunomodulatory effects of Azithromycin in addition to standard 2HRZE/4HR treatment in TB patients.

Specific Objective 3: Determine the effect of Azithromycin in addition to standard care on lung function and morphology.

Purpose and objective(s)

AZT-TB is a clinical pilot study to evaluate the immunomodulatory effects of Azithromycin in pulmonary tuberculosis (TB) patients. The hypothesis is that Azithromycin in conjunction with standard care improves pulmonary health in TB patients by inhibiting proinflammatory cytokines. By minimizing the body's own inflammatory response, patients will have less scarring in the lungs, and this will prevent persistent lung damage as a result of TB.

Adult patients with active TB will receive the standard HRZE treatment (control group, n= 50 patients) or Azithromycin in addition to standard care (experimental group, n=50 patients). In follow-up visits (week 2, month 1, month 2, month 6 and month 12) overall health will be assessed, biological samples will be collected (sputum and serum) and pulmonary health will be evaluated.

Study description

Study site

The Referral Centre Antituberculeux located in Brazzaville, Republic of the Congo will be the site of recruitment, diagnosis and treatment of all recruited patients. After signed informed consent obtained, blood samples and sputum will be collected. After centifugation, serum will be kept at -20°C until further analysess consisted on serum inflammatory markers assessment at the Centre de Recherches sur les Maladies Infectieuses (CeRMI-FCRM, Republic of Congo. Clinical and demographic information of each study participant will be collected in the case report form (CRF).

TB diagnosis

In accordance with the WHO guidelines, both X-ray, as well as sputum-based tests including sputum smear microscopy, *M. tuberculosis* culture and Xpert MTB/RIF (only at baseline) will be performed to diagnose active TB, and monitor the disease development in the current study.

Study design

A prospective, randomized study will be performed to assess the immunomodulatory effect of Azithromycin in TB patients (see **Figure 1 study design**). Sputum smear microscopy, Xpert MTB/RIF, Mtb culture and chest X-Ray will be performed to diagnose for pulmonary TB in patients with symptoms suspicious of TB (including coughing >two weeks, weight loss, fatigue, fever, night sweats). Line probe assay (LPA) will be performed using the commercially available Genotype MTBDR plus assay, to exclude patients with drug-resistant TB from the study. HIV test will be performed according to TB management guidelines and HIV positive patients excluded from the study. The patients will be enrolled after consent and ethical approval. After randomization, patients will be treated with standard of care (2HRZE/4HR) or with Azithromycin on top of standard 2HRZE/4HR treatment. The study will be conducted as open-label study. Azithromocyin will be administered at an initial dose of 500 mg followed by 250 mg once daily for 28 days as film-coated tablet. The patients in both treatment arms will be stratified based on disease severity, age and sex. Patients will be recruited over a period of 12 months and will be followed for 12 months. We will enrol 50 adult (> 18 years old) with a first episode of pulmonary TB and living in Brazzaville. Lung manifestations will be evaluated at each follow-up consult using chest X-ray and a pulmonary function test.

Number of arms: 2 (Experimental arm which receives AZT and Control arm without AZT) Both groups will be enrolled at the same facility and as much as possible matched for age and sex.

Method of allocation: Randomized. The patients in the two study arms will be randomized and stratified based on disease severity, age and sex.

Randomization will be manual .

Masking: none (open label)

Intervention:

Experimental Azithromycin arm

Patients in this arm will be treated with azithromycin 250 mg once daily for 28 days on top of standard HRZE treatment. An azithromycin loading dose of 500 mg (two tablets of 250 mg) will be administered on day 1.

Control Standard of care arm

Patients in this arm will receive no additional treatment on top of standard HRZE treatment. The HRZE treatment includes Isoniazid (5 mg/kg daily), Rifampicin (10 mg/kg daily), Ethambutol (25 mg/kg daily) and Pyrazinamide (30 mg/kg daily) for 2 months followed by Isoniazid (5 mg/kg daily) and Rifampicin (10 mg/kg daily) for 4 months.

Primary and secondary outcome measures

Primary Outcome Measures : *Pulmonary presentation and serum inflammatory markers (cytokine levels)*

1. Radiological marker; Chest X-ray abnormalities [Time Frame: Before randomization, week 2, month 1, month 2, month 6 and month 12]

2. Pulmonary function. Lung function test [Time Frame: Before randomization, week 2, month 1, month 2, month 6 and month 12]

3. Inflammatory markers. Serum inflammatory cytokines (*(IL-2, IL-4, IL-10, IFN-γ, and TNF-α)* [Time Frame: Before randomization, week 2, month 1, month 2, month 6 and month 12]

Secondary Outcome Measures: sputum conditions

1. Sputum inflammatory cytokines (*(IL-2, IL-4, IL-10, IFN-γ, and TNF-α)*
   [Time Frame: Before randomization and week 2, month 1, month 2, month 6 and month 12]

2. Serum white blood cells [Time Frame: Before randomization and week 2, month 1, month 2, month 6 and month 12]

3. Sputum inflammatory cell counts [Time Frame: Before randomization and week 2, month 1, month 2, month 6 and month 12]

Other Outcome Measures:

1. Evaluation of disease progression [Time Frame: Up to 12 months]

2. Evaluation of overall health [Time Frame: Before randomization and week 2, month 1, month 2, month 6 and month 12]

Schedule for study conduct including timelines for key study milestones

The total duration of the clinical pilot study will be 24 months, from October 2021 until October 2023. Ethics/regulatory approval will be obtained in September 2021. Patients will be recruited over a period of 12 months, from October 2021 until October 2022. Intervention follow up visits will be at week 2, month1, month 2, month 6 and month 12.

Schedule for clinical study:
First patient, first visit: October 2021
Last patient, first visit: October 2022
Last patient, last visit: October 2023
Planned 25% patient enrolment: January 2022
Planned 50% patient enrolment: April 2022

Planned 75% patient enrolment: July 2022

Final database lock: December 2023

Study analysis: from April 2022 until January 2024

Availability of final study report: January 2025

Study closure: January 2025

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Product(s) to be tested and supply (where applicable)

Product name	**Manufacturer**	**Details of product (approved for use/under development), GMP guarantee, supply and availability – see details above)**
Generic name: Azithromycin Brand name: Zithromax	Pfizer	Azithromycin 250 mg Tablets • Each film-coated tablet contains: 250 mg of azithromycin (as monohydrate) and 0.36 mg soya lecithin. Azithromycin has been approved for the following bacterial infections: • acute bacterial sinusitis (adequately diagnosed) • acute bacterial otitis media (adequately diagnosed) • pharyngitis, tonsillitis • acute exacerbation of chronic bronchitis (adequately diagnosed) • mild to moderately severe community acquired pneumonia • skin and soft tissue infections • uncomplicated Chlamydia trachomatis urethritis and cervicitis

		Pfizer has all the necessary certificates for GMP guaranteed production of Azithromycin. Agreement with Pfizer for supply of these tablets has not been made yet, but will be made at the start of the AZT-TB project. Availability of Azithromycin should not be a problem.

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Study population

Study population

We will enroll 100 adults (> 18 years old) of both sex with a first episode of pulmonary TB, HIV-negative, sensitive to all first line drugs and living in Brazzaville. The patients in both treatment arms will be matched for disease severity, age and sex as much as possible. Fifty patients will be enrolled in each arm.

Inclusion criteria

- > 18 years old
  Clinical diagnosis of drug sensitive pulmonary tuberculosis (molecular test; identification Mtb complex; absence of resistance genes such as rpob, inha, katg)
  No pregnant women confirmed by a pregnancy test.
- Written informed consent

Exclusion criteria

- Patient reported previous history of treatment for tuberculosis
- Patients younger than 18 years
- Pregnancy or breast feeding
- Patients with hypersensitivity to macrolide antibiotics

- Treatment with any macrolide in the previous month
- Treatment with any tetracycline in the previous month
- Treatment with any inhaled or oral corticosteroid in the previous month
- Concomitant treatment with analgesic (NSAIDs)/immunosuppressant drugs (except paracetamol)
- Treatment with digoxin
- Patients with gastrointestinal complaints, like diarrhea and vomiting (≥grade 2, observed)
- Patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of Azithromycin.
- Other known respiratory diseases, including bronchiectasis, pulmonary fibrosis, pulmonary vascular disease or lung cancer
- HIV infection or AIDS

Statistical analysis planning and power calculations (sample size)

Statistical methods

Quantitative variables will be presented as the mean standard deviation or the median and qualitative variables as percentage.

Analysis of the primary point:

Non-inferiority will be established if the upper limit of the two-sided 95% confidence interval of the difference in the proportion of 6-month negative sputum rate between the two groups (Control arm - Experimental arm) is lower than the non-inferiority margin (10%). Intention-to-treat analysis will be performed followed by a per protocol analysis. A multiple imputations analysis will be performed if more than 5% of the data are missing for the primary endpoint. Farrington-Manning p-value for non-inferiority will be calculated and a two-sided p-value < 0.05 will be required for statistical significance.

Radiological , lung function or immunological outcomes will be measured as follows:

1) Chest X-ray abnormalities evaluation

All chest radiograms were interpreted by an experienced radiologist, not engaged in the therapeutic process. The chest X-ray will be divided into three levels: 1) the bronchial bifurcation, 2) the upper level of the diaphragm, and 3) halfway between levels 1) and 2). Each area will be calculated as follows: Grade 0, no opacity; Grade 1, <5% opacity; Grade 2, 5-24% opacity; Grade 3, 25-49% opacity; Grade 4, 50-74% opacity; and Grade 5, >75% opacity. The total score will be calculated as the sum of the scores for the six areas.

2) Measurement of pulmonary function

- Pulmonary function will be measured using a dry rolling seal spirometer (Model 2130; Sensor-Medics, Yorba Linda, CA, USA) according to the American Thoracic Society/European Respiratory Society criteria for standardization (12). Spirometry data obtained on site by clinical technicians will transferred to an internet review center for processing. The data will be compared against criteria metrics for acceptability, reproducibility, and quality control. A principal investigator will be validated and stored the data in a KCDC repository management system.
- AFO will be defined by a decrease of the pre-bronchodilator forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) below 70%. Severity of AFO will classified by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage system. Prebronchodilator FEV1/FVC ≥ 70% and FVC < 80% will defined as spirometry restriction.
- Residual pulmonary function will be determined by subtracting the predicted from the measured value; with reference to the Framingham Study (2). Univariate relationships with residual lung function measures will examined by Pearson's correlation.

Spirometry measurements

The ATS / ERS recommendations will be used as follows:

- Normal spirometry when FEV1 ≥80%, FVC ≥ 80%, and FEV1 / FVC> 70% of predicted values.

- Obstructive ventilatory disorder when FEV1 / FVC ≤70% and FVC> 80% of predicted values.

- Restrictive ventilatory disorder when FEV1 / FVC> 70% and FVC <80% of predicted values.

- Mixed ventilatory disorder when FVC <80% and FEV1 / FVC <70% of predicted values.

The degree of severity was classified according to FEV1:

- Light when FEV1 ≥70%.
- Moderate when the 70% <FEV1 ≥50%.
- Severe when FEV1 <50%.

3) Measurement of serum inflammatory cytokines will be done by ELISA using commercial kits.

Analyses of secondary endpoints:

- *Sputum inflammatory cell percentage will compared between two arms with a Fisher exact test as appropriate, at week 2, month 1, month 2, month 6 and month 12.*

- *Classification of white blood cell counts will do into quartiles over the normal range.*

- *White blood cell counts and pulmonary function tests will correlated by multiple regression models and trends testing at week 2, month 1, month 2, month 6 and month 12.*

- *Release of inflammatory biomarkers will analysed as follows: Dunnett's multicomparison, nonparametric, test to compare the Experimental Azithromycin arm group versus the Control Standard of care arm.*

Other Outcome Measures:

- *The regression parameters will differentiate the converters and the non-converters up to 12 months.*

- *Associations between the evaluation of overall health and the variables investigated will analyzed through the Wald's test. For crude and adjusted analysis, we calculated the prevalence ratios and their respective confidence intervals of 95% (95%CI), by means of Poisson regression, adjusted for complex designs.*

Correlation between variables will be assessed using Spearman's rank correlation coefficient. Statistical analysis will be performed using IBM SPSS version 26.

Calculation of sample size

Our study will compare two means.

Level of significance = 5%, Power = 80%, Zα = Z is constant set by convention according to accepted α error and Z (1-β) = Z is constant set by convention according to power of study which is calculated from Formula of calculating sample size is:

$n = 2 (Z\alpha + Z [1-\beta])^2 \times SD^2 / d^2$

$Z\alpha = 1.96$, $Z (1-\beta) = 1.28$

SD = 15, d (effect size) = 11

So $n = 2 (1.96 + 1.28)^2 \times 225 / 256 = 39.04$

40 individuals in each group should be recruited in the study.

A recent study reported a rate of loss to follow up among tuberculosis patients in the Republic of Congo of 34.1% (1).Which corresponds to about 7 patients that will have to be added to our sample size.

Finally our **sample size will be 100 or 50 for each group.**

Roles and responsibilities of the Data and Safety Monitoring Board (DSMB)

The DSMB will be formed and will be composed of independent experts to advise; they will responsible for defining its deliberative processes, including: event triggers that would call for an unscheduled review, stopping procedures that are consistent with the protocol, unmasking (unblinding), and voting procedures.

The membership of the DSMB will reflect the biological and medical specialties necessary to interpret the data from the clinical trial and to fully evaluate participant safety. We do not expect safety problems as the toxicity of Azithromycin 250mg is well known.

Recruitment strategy and retention

Patients (n=100) from the Referral Centre Antituberculeux located in Brazzaville, Republic of the Congo suffering from active TB will be recruited for this clinical pilot study.
100 Patients that meet the inclusion and exclusion criteria will be enrolled in this study.
A previous clinical study conducted at the same site was able to recruit 725 patients with TB in one year, so I don't foresee problems to recruit 100 patients over the course of one year *(2)*.
The loss to follow up among TB patients in Congo is ~34% (1). I have taken this into account when designing the study (see statistical analysis).
We don't expect problems with compliance. TB patients are quite ill and are motivated to become better. The standard of care is an intense regime of a mixture of antibiotics administered for 6 months. The 28 days of a low dose of Azithromycin given during the first period of treatment will have minimal (if any) side effects compared to the standard care.

Recruitment site selection

Globally, an estimated 10.0 million people fell ill with TB in 2018, a number that has been relatively stable in recent years. The burden of disease varies enormously among countries, from fewer than five to more than 500 new cases per 100 000 population per year, with the global average being around 130. Geographically, Africa accounts for ~24% of all TB cases. The Republic of Congo is one of 22 countries considered a 'high burden' country for TB. The incidence and prevalence in Republic of Congo are respectively 382 per 100 000 and 462 per 100 000. The recruitment site for the AZT-TB clinical pilot study is the Referral Centre Antituberculeux located in Brazzaville, Republic of the Congo. In a previous study executed

at this center in Brazzaville 725 TB patients were enrolled in a clinical study in 12 months time *(2)*.

There is fruitful collaboration between the FCRM and the TB referral center in place: we previously collaborated on another project. As a result, a clinical study infrastructure has been established for years.

Patient and/or community involvement

We will actively seek out involvement of farm groups or cattle-breeding workers as these people have an increased risk to develop TB: Farm workers are approximately six times more likely to develop tuberculosis (TB) than the general population of employed adults. Their input on the study design will be very valuable, as they know (often from first hand) how important proper treatment is and how persistent lung damage can affect quality of life.

Clinical Study Sponsor

The current clinical pilot study will be an investigator initiated study sponsored by The Congolese Foundation for Medical Research (FCRM).

Ethical and regulatory approval

Clinical research in Republic of Congo are regulated by the Congolese Ministry of Health and population. Our clinical research will comply with this to gain approval by the Institutional Committee of the FCRM.

Our clinical study will comply with Good Clinical Trial Practice standards.

The waiting time is one month after filing of the file with the ethics committee.

Type of approval

The type of clinical investigation approval process is Sequential. I will apply both to Ethics committee and scientific committee at once but the final approval for the trial will be only after the Ethics committee's approval.

Regulatory Approval Process

Pre-Approval

I need to get approval from the ethics committee before applying to the BPOM for permission to begin a clinical trial, which conducts the scientific and ethical review of the clinical trial documents.

After the approval of the ethics committee, BPOM will evaluate the clinical trial documents in consultation with a national team of clinical trial experts and granted approval or rejection within twenty days of the submission.

Patient Recruitment

Ethics in Clinical Research

This trial study is to develop generalizable knowledge that improves patient health. The path to finding out if Azithromycin + standard care is more effective in improving pulmonary health than standard care alone.

Some of the influential codes of ethics and regulations that guide ethical clinical research include: Nuremberg Code (1947) and declaration of Helsinki (2000).

Fair subject selection

Consistent with the scientific purpose, people will be chosen in a way that minimizes risks and enhances benefits to patients and society. Patients who will accept the risks and burdens of research will be in a position to enjoy its benefits, and those who may benefit will share some of the risks and burdens.

Favorable risk-benefit ratio

Everything will been done to minimize the risks and inconvenience to research patients, to maximize the potential benefits, and to determine that the potential benefits to patients and Congolese society are proportionate to, or outweigh, any risk or burden.

Independent review

Potential conflicts of interest will minimized. An independent reviewing panel with no vested interest in the study will review the proposal and ask important questions, including: Are those conducting the trial sufficiently free of bias? Is the study doing all it can to protect research volunteers? Has the trial been ethically designed and is the risk–benefit ratio favorable?

Informed consent

Individuals will give informed consent in which individuals (1) are accurately informed of the purpose, methods, risks, benefits, and alternatives to the research, (2) understand this information and how it relates to their own clinical situation or interests, and (3) make a voluntary decision about whether to participate.

Respect for potential and enrolled subjects

Individuals will be treated with respect from the time they will approached for possible participation—even if they refuse enrollment in a study—throughout their participation and after their participation ends. This includes:

Respecting their privacy and keeping their private information confidential.

Respecting their right to change their mind, to decide that the research does not match their interests, and to withdraw without penalty.

Informing them of new information that might emerge in the course of research, which might change their assessment of the risks and benefits of participating.

Monitoring their welfare and, if they experience adverse reactions, untoward events, or changes in clinical status,

Ensuring appropriate treatment and, when necessary, removal from the study.

Informing them about what was learned from the research.

Clinical Study Registration

This pilot clinical study will be registered in the Pan African Clinical Trials Registry (www.pactr.org) or other platform.

Study safety

The use of Azithromycin apposes no risks to the safety of the patients enrolled in this study. The toxicity of this drug has been thoroughly investigated and patients at risk will be excluded in this project.

The AZT-TB study apposes no risk to the staff conducting the study.

Details of the Target Product Profile (TPP)

A safe add-on therapy for active TB patients that minimizes or prevents persistent lung damage.

Details of the products to be tested (composition, stability, prior safety data etc)

Azithromycin is registered in USA, UK, South Africa and most other developed countries (except Central Eastern Europe) as Zithromax, Pfizer. Zithromax is a macrolide antibacterial drug indicated for mild to moderate infections caused by designated, susceptible bacteria. Azithromycin has unique pharmacokinetic and pharmacodynamic features, resulting in high and sustained intracellular tissue concentrations and relatively low circulating concentrations (35). The absolute bioavailability of azithromycin 250 mg capsules is 38%. It is metabolized via hepatic pathways other than cytochrome P450, thereby minimizing the risk of drug-drug interactions. Compared with other macrolide antibiotics, it offers improved efficacy and safety. As a result, it is used for the treatment of many types of bacterial infection, specifically respiratory infections.

Azithromycin is generally well-tolerated but has relatively common adverse effects. These adverse effects include diarrhea (5 to 14%), nausea (3 to 18%), abdominal pain (3 to 7%),

or vomiting (2 to 7%). Patients will be closely monitored for the development of these and other side-effects. Treatment with Azithromycin will be discontinued when serious allergic and skin reactions or hepatotoxicity are observed.

Drug information: https://druginfo.nlm.nih.gov/drugportal/name/Azithromycin

Possible side effects of Azithromycin

- Cardiovascular risks, , skin reactions, patients with hepatic insufficiency will be carefully screened.

Contre-indications for Azithromycin

- Patients with known hypersensitivity to Azithromycin, Erythromycin, any macrolide or ketolide drug.
- Patients with a history of cholestatic jaundice/hepatic dysfunction associated with prior use of Azithromycin.

Details of the regulatory strategy and of any consultation with/advice received from regulators (e.g. European Medicines Agency) and/or from WHO.[CC2]

The AZT-TB trial has not yet been submitted to the regulatory authorities since the detailed design may change. All local, national and EU regulatory and ethical approvals needed for performing the proposed clinical trial will be available before initiation and inclusion of the first patient in the clinical study. Regarding details on regulatory strategy: I will (1) Submit the study protocol to the ethics committee, and (2) After project evaluation and ethical approval, submit the approved study project to the Ministry of Health and Population for administrative authorization. Previously in the CANTAM project (2009-2014), we followed the same procedure for the regulation strategy.

Study management

This investigation will be conducted in Brazzaville, Congo, following approval by National Competent Authority and local Ethic Committees. Under the supervision of my mentor Prof.

Ntoumi, I will be responsible for management of the clinical study. A trial Steering Committee will be formed that includes an independent chair, two independent members, two collaborators and two members of the public. There will be a clinical coordinator of study, a co-investigator, medical advisor, a lab technician, a data manager, data center clean, and a statistician. Together with the sponsor (FCRM) I will seek specific advice from the DSMB on aspects of study procedures. The responsibility for reporting the deliberation of the DSMB is from the chair of the DSMB to the sponsor, and the responsibility for liaising with investigators and ethics committees lies with the sponsor.

Study monitoring and quality control

Following pre-study visits and site initiation visits, inclusion of subjects is foreseen at month 12 of the project. I will monitor the clinical pilot study through repeated site monitoring visits to ensure adherence to the clinical study protocol and correct and complete collection of data. Furthermore, together with DSMB I will monitor the progress of the trial, trial safety and compliance with all regulatory rules and with ethics.

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