Safety of Rifampicin at High Dose for the Treatment of Adult Subjects with Complex Drug Susceptible Pulmonary and Extrapulmonary Tuberculosis

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Primary Objective: To evaluate the safety of high-dose rifampicin (35 mg/kg/d) supplemented with standard doses of isoniazid, pyrazinamide, and ethambutol for 8 weeks in adult subjects with pulmonary or extrapulmonary DS-TB belonging to difficult to...

Ethical review	Approved WMO
Status	Pending
Health condition type	Mycobacterial infectious disorders
Study type	Interventional

Summary

ID

NL-OMON52031

Source
ToetsingOnline

Brief title
RIAlta study

Condition

- Mycobacterial infectious disorders

Synonym
Tuberculosis

Research involving
Human

Sponsors and support

Primary sponsor: Vall d□Hebron University Hospital

Source(s) of monetary or material Support: Enose Company, Zutphen, The Netherlands,European Commission (RISE;Marie Curie Horizon 2020);grant number 823890

Intervention

Keyword: Complex Tuberculosis, High-dose rifampicin, Pharmacokinetics

Outcome measures

Primary outcome

Primary safety endpoint: the proportion of participants with one or more SAE (grade 3 or superior) at the end of the intensive phase (first 8 weeks of treatment).

Secondary outcome

Secondary safety endpoints:

* Proportion of participants with any adverse event (tolerability endpoint).

* Proportion of participants needing to stop the study regimen for any reason other than microbiological ineligibility.

* Sensitivity analyses of the primary safety endpoint assuming all losses to follow-up and non-tuberculosis deaths have an unfavorable outcome and assuming all losses to follow-up and non-tuberculosis deaths have a favorable outcome.

Secondary efficacy endpoints:

* Proportion of participants who have sputum culture conversion at 8 weeks after treatment onset or proportion of participants with clinical and radiological improvement (if follow-up images are available for extra-pulmonary TB) but without a follow up sample at 8 weeks after treatment onset.

* Proportion of participants who suffer a relapse at 1 year after treatment

completion.

* Time to sputum culture conversion.

* Time to negative sputum smear.

* Time to negative smell print test using an eNose device.

* Distribution of time to sputum culture positivity.

* Distribution of time to sputum smear bacterial load decrease (see the SOP for standard procedures for bacterial counting on a sputum smear).

* Correlation of the AUC/MIC values with time to sputum culture conversion, sputum smear conversion, time to sputum culture positivity and sputum smear bacterial load decrease.

* Sensitivity analyses will be performed for the secondary efficacy endpoints assuming all losses to follow-up and non-tuberculosis deaths have an unfavorable outcome and assuming all losses to follow-up and non-tuberculosis deaths have a favorable outcome.

* Mean difference in SF-12 and St George*s respiratory questionnaire scores at 0 and 8.

* Proportion of participants who are classified as having a failure during treatment and relapse after completion of full treatment regimen and first year of follow up.

Study description

Background summary

Tuberculosis (TB) is an infectious disease caused by Mycobacterium tuberculosis. TB primarily affects the lungs but can also cause disease in

other organs. In humans, TB is spread by airborne droplets originating from a contagious individual while coughing or sneezing.
TB causes more deaths worldwide than any other infectious disease. In 2018, an estimated 10 million people developed TB and 1.4 million died from TB. Globally, TB is not uniformly distributed. TB hits harder in developing and underdeveloped countries which contribute to more than 95% of total diagnosed cases. Rapid TB diagnosis is based on molecular and microscopic detection of M. tuberculosis bacilli in biological specimens from patients (sputum, cerebrospinal fluid, pleural fluid, lymph node aspirate among others). In the absence of microscopic and/or molecular evidence, TB is also diagnosed based on the clinical picture, epidemiological data, and morphologic features (radiological or histological). The growth of M. tuberculosis on solid or liquid culture media remains the gold standard confirmatory test, and the colonies are utilized for phenotypic drug susceptibility testing. The time to sputum culture conversion in liquid media is utilized frequently in clinical trials as a proxy marker to predict therapeutic efficacy in pulmonary TB.

Therapeutic rationale

By the late 1970s, after a series of trials conducted by the Medical Research Council, the best drug combinations and the duration of treatment required were worked out. The best results were achieved using an *intensive* phase of 2 months rifampicin, isoniazid and pyrazinamide, ethambutol followed by a *continuation* phase of 4 months rifampicin and isoniazid. Rifampicin is the backbone drug in the treatment of DS-TB due to its potent bactericidal and sterilizing activity. The 10 mg/kg dose was selected for rifampicin based on pharmacokinetic, toxicity and cost concerns. The cure rate is estimated at 83% in HIV negative patients and 78% in HIV-associated TB. Current research results show that for a concentration dependent drug like rifampicin, doses towards the upper end of therapeutic window achieve optimal sterilizing activity and prevent spontaneous mutations related with acquired drug resistance. It is now widely accepted that rifampicin is currently under-dosed. This has been shown in murine models and in phase I and phase II clinical studies. In the mouse models published by Rosenthal and colleagues (doses up to 40mg/kg), Hu and colleagues (doses of up to 50mg/kg) and), and Steenwinkel and colleagues (doses up to 160mg/kg/day), a higher rifampicin exposure resulted in a faster and complete sterilization of visceral cultures. In the studies by Boeree and colleagues, higher rifampicin doses achieved up to 10-fold higher exposure in plasma, resulting in a faster time to stable culture conversion in liquid media in the 35mg/kg rifampicin group than in the 10mg/kg group, and these doses were safe and well tolerated. The hollow fiber study by Gumbo and colleagues evaluated the relationship between rifampicin exposure, microbial kill of log-phase growth and suppression of mutant population and concluded that higher rifampicin doses than those currently used would optimize the effect of rifampicin. Therefore, increased doses might have the potential to shorten DS-TB treatment.
In 2014, the WHO member states endorsed the End TB strategy that has three main

objectives to be accomplished by 2035 compared to the data from 2015: to reduce the number of TB related deaths by 90%, to reduce TB incidence by 80% and to eliminate the catastrophic costs associated to TB. In order to achieve these objectives, the WHO stresses the need of developing innovative ways to deliver the already available resources as well as the need of developing new treatment, preventive and diagnostic strategies.

Participant population rationale

DS-TB treatment success rate varies greatly between countries and among patient*s subgroups. In 2017, treatment success rate of 85% was reported for new cases of TB with the standard treatment composed of rifampicin, isoniazid, pyrazinamide, and ethambutol. This regimen combines early bactericidal activities of isoniazid and rifampicin with rapid sterilizing activities conferred by rifampicin and pyrazinamide. Nevertheless, treatment outcomes are worse in certain patient subpopulations such as those with diabetes, liver disease, persons living with HIV and CNS involvement. As an example, in 2017 success rate was 75% for persons living with HIV. The outcomes of these difficult to treat patients could be improved using higher doses of rifampicin, as suggest the results of a trial by Ruslami and colleagues, in which doses of 13 mg/kg with isoniazid and pyrazinamide improved 6-month survival rate in Indonesian patients with TB meningitis, without an increased risk of toxicity. Data from clinical daily practice on high-dose rifampicin for a full 6- to 12-month treatment course adds on to the available body of evidence suggesting that higher doses (32 mg/kg) are safe and well tolerated in difficult to treat TB patient population.

Rifampicin dose administration rationale

A retrospective observational cohort of 88 patients from Dekkerswald center in the Netherlands with difficult-to-treat TB or initial low rifampicin plasma levels (Cmax of <8 mg/L or AUC0-24 <41mg/L) treated with 20-32 mg/kg of rifampicin, showed that high dose rifampicin was safe and well tolerated. All patients completed 6-12 months of treatment with high dose rifampicin, without an increase in rifampicin related adverse events. However, the safety and tolerability of higher rifampicin doses need further validation in prospective and adequately powered clinical studies before it can be recommended in the WHO guidelines for wide use in programmatic settings, especially in patients with a higher risk of toxicity. The randomized phase II trial in Peruvian patients by Velásquez et al. showed higher sterilizing activity with no significant differences in safety with doses of 15 and 20mg/kg as compared to standard doses. In the study by Ruslami et al., high dose rifampicin showed an important reduction of mortality in severely ill patients with TB meningitis. Both studies excluded patients with extrapulmonary disease and, both cohorts together, only 6 patients were living with HIV and 5 had diabetes. The results of these studies suggest that higher doses of rifampicin could help to shorten TB treatment, although this needs to be investigated in large phase III trials

after we have collected sufficient evidence about the safety and tolerability of the higher dosages in a wider variety of patients.
Therefore, this study will evaluate high dose rifampicin (35 mg/kg) in combination with standard doses of isoniazid, pyrazinamide and ethambutol in difficult to treat TB patients, for the first 8 weeks of treatment, as this period seems to be in which most of the bacterial killing and sterilization take place. Clearance of M. tuberculosis bacilli from the sputum and culture conversion during the first two months of treatment serve as a proxy for evaluating survival rate and cure in DS-TB patients, although the cure definition for DS-TB from the WHO requires a negative smear or culture at the end of treatment and there is some evidence that a follow-up after the end of treatment enhances the detection of treatment failure.

Study objective

Primary Objective:
To evaluate the safety of high-dose rifampicin (35 mg/kg/d) supplemented with standard doses of isoniazid, pyrazinamide, and ethambutol for 8 weeks in adult subjects with pulmonary or extrapulmonary DS-TB belonging to difficult to treat subgroups.

Secondary Objective(s):
1. To evaluate the tolerability of high-dose rifampicin (35 mg/kg/d) supplemented with standard doses of isoniazid, pyrazinamide, and ethambutol for 8 weeks in adult subjects with pulmonary or extrapulmonary TB belonging to difficult to treat patient subgroups.

2. To evaluate the efficacy of high dose rifampicin (35 mg/kg/d) supplemented with standard doses of isoniazid, pyrazinamide, and ethambutol for 8 weeks by assessing early sterilizing activity in the sputum of pulmonary TB subjects belonging to difficult to treat patient subgroups.

3. To compare the bactericidal activity as the proportion of sputum smear conversion at 8 weeks.

4. To compare the time dynamics of sputum smear bacterial load decline, smear and culture conversion.

5. To compare the relapse rate 1 year after treatment completion (extended follow up).

6. To describe pharmacokinetics-pharmacodynamics (PK/PD) of rifampicin at high doses in difficult-to-treat pulmonary and extrapulmonary TB.

7. To describe the association between genetic polymorphisms and differences in AUC of rifampicin.

8. To analyse the correlation between the AUC/MIC values and the efficacy outcomes.

9. To evaluate the response to treatment as measured by exhaled VOCs by means of an electronic nose device, the AeoNose*.

10. To describe tuberculosis associated costs and the quality of life of DS-TB participants

Study design

This is a phase IIb, interventional, open-label, multi-center, prospective clinical study of high dose rifampicin (35 mg/kg, intervention group) versus standard-dose (10mg/kg/day, historical group). High dose rifampicin (35 mg/kg/day) will be given open label during the first 8 weeks of treatment course supplemented with standard doses of isoniazid, pyrazinamide, and ethambutol according to the national guidelines and local protocols from the different participating countries.

Intervention

High dose rifampicin (35 mg/kg) will be given once daily for 8 weeks. After 8 weeks, participants will be switched to the standard of care as per the local and national guidelines. Visits, diagnostic and follow-up tests, questionnaires, and other interventions will be performed as summarized in the study flow chart in the protocol.
We will whole blood and Dried Blood Spot (DBS) samples to analyze both pharmacokinetics and pharmacogenetics. To assess pharmacokinetics, we will use a limited sampling strategy (3 time points after drug dosing) in all participants per site at week 4 of treatment. The same DBS samples will be used to conduct a study on genetic polymorphisms and correlate these results with the safety and tolerability data and with PK and PD data.
We will also assess quality of life and TB associated costs, using SF-12 (all participants), the St George*s respiratory questionnaire (for pulmonary TB participants) and the *EUSAT-RCS developed tool* to estimate TB associated costs (up to 15 participants from the experimental arm per site, see below).

Study burden and risks

Therapeutic rationale

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backbone drug in the treatment of DS-TB due to its potent bactericidal and sterilizing activity. The 10 mg/kg dose was selected for rifampicin based on pharmacokinetic, toxicity and cost concerns. The cure rate is estimated at 83% in HIV negative patients and 78% in HIV-associated TB. Current research results show that for a concentration dependent drug like rifampicin, doses towards the upper end of therapeutic window achieve optimal sterilizing activity and prevent spontaneous mutations related with acquired drug resistance. It is now widely accepted that rifampicin is currently under-dosed. This has been shown in murine models and in phase I and phase II clinical studies. In the mouse models published by Rosenthal and colleagues (doses up to 40mg/kg), Hu and colleagues (doses of up to 50mg/kg) and), and Steenwinkel and colleagues (doses up to 160mg/kg/day), a higher rifampicin exposure resulted in a faster and complete sterilization of visceral cultures. In the studies by Boeree and colleagues, higher rifampicin doses achieved up to 10-fold higher exposure in plasma, resulting in a faster time to stable culture conversion in liquid media in the 35mg/kg rifampicin group than in the 10mg/kg group, and these doses were safe and well tolerated. The hollow fiber study by Gumbo and colleagues evaluated the relationship between rifampicin exposure, microbial kill of log-phase growth and suppression of mutant population and concluded that higher rifampicin doses than those currently used would optimize the effect of rifampicin. Therefore, increased doses might have the potential to shorten DS-TB treatment.
In 2014, the WHO member states endorsed the End TB strategy that has three main objectives to be accomplished by 2035 compared to the data from 2015: to reduce the number of TB related deaths by 90%, to reduce TB incidence by 80% and to eliminate the catastrophic costs associated to TB. In order to achieve these objectives, the WHO stresses the need of developing innovative ways to deliver the already available resources as well as the need of developing new treatment, preventive and diagnostic strategies.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The participant must fulfill either criteria nr. 1-4 AND nr. 5 OR criteria nr. 1-4 AND 6, AND anyone of 7-14:
1. Subjects with confirmed or probable pulmonary or extra pulmonary DS-TB.
2. Informed consent provided.
3. Positive smear, positive Xpert MTB/RIF test, positive M. tuberculosis culture (confirmed cases) OR histological study compatible with necrotizing granulomas OR a liquid biochemistry (pleural, pericardial, ascites or cerebrospinal fluid) suggestive of TB together with clinical symptoms resembling TB disease in the absence of any other possible cause (probable cases).
4. Female participants of childbearing age must have a negative pregnancy test at baseline.
AND
5. Age >= 60 years old.
OR
6. Age >= 18 years
AND one of the following
7. Body mass index <= 18.5
8. Human Immunodeficiency Virus (HIV) infection.
9. Diabetes Mellitus
10. Hepatitis C virus (HCV) infection (positive HCV serology)
11. Hepatitis B virus (HBV) infection (positive HBV surface antigen)
12. Daily alcohol intake >= 2 units of alcohol (1 unit of alcohol: 4% alcohol 250ml (ie beer); 4.5% alcohol 218ml (i.e. cider); 13% alcohol 76ml (i.e. wine); 40% alcohol 25ml (i.e. whisky))
13. Chronic liver disease of any other cause (metabolic, toxic, autoimmune)
14. Central Nervous System TB involvement

Exclusion criteria

Subjects will be excluded from entry if ANY ONE of the criteria listed below is met:
1. Rifampicin resistance confirmation.
2. Barthel index < 40 for subjects older than 60 years old.
3. Signs of liver disease not related to TB [Liver enzymes (AST or ALT) > 5x upper limit of normal , Total bilirubin > 5x upper limit of normal, Patients with a Child-Pugh grade C cirrhosis or acute decompensation of their chronic liver disease at enrolment.]
4. Subjects with known allergy or sensitivity to rifampicin, or any of the other components of DS-TB treatment.
5. Treatment with any of the following: rifampicin, isoniazid, pyrazinamide, ethambutol, levofloxacin, or moxifloxacin within the last month for at least 14 days or current TB treatment for more than 7 days.
6. The subject is enrolled in any other investigational trial that includes a drug intervention.
7. Subjects with solid organ transplantation or bone marrow transplantation.
8. Subjects with an active onco-hematological neoplasm.
9. Previous severe pulmonary disease, other than pulmonary DS-TB, according to local investigator.
10. Pre-existing epilepsy or psychiatric disorder according to local investigator.
11. Ischemic heart disease OR severe arrhythmia within 6 months OR Atrial Fibrillation with oral anticoagulant therapy indication when transitioning to low-molecular weight heparin is not feasible.
12. Positive pregnancy test
13. Breastfeeding women.
14. The subject used any drugs or substances known to be strong inhibitors or inducers of cytochrome P450 enzymes which are involved in the degradation pathways of rifampicin within the time windows specified in the protocol.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-11-2020
Enrollment:	40
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	NA
Generic name:	Rifampicin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	07-09-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-11-2023
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-003146-36-NL
CCMO	NL75346.091.20