Pragmatic trial on the safety and tolerability of an optimized dose of rifampicin in tuberculosis patients

Published: 11-04-2022
Last updated: 30-01-2025

This study has been transitioned to CTIS with ID 2023-509885-39-00 check the CTIS register for the current data. The primary objective is to describe and compare the incidence of hepatotoxicity in standard care and in a regimen with an optimized...

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

Summary

ID

NL-OMON53704

Source
ToetsingOnline

Brief title
PORT: Pragmatic Optimized Rifampicin trial

Condition

- Mycobacterial infectious disorders

Synonym
tuberculosis

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: pragmatic, Rifampicin, safety, tuberculosis

Outcome measures

Primary outcome

The primary endpoint is the incidence of hepatotoxicity, which will be compared between treatment arms at the end of the 6 months treatment.

Secondary outcome

Secondary endpoints are:

• The proportion of adverse events overall and graded by severity assessed to be related or probably related to rifampicin during the 6 months treatment will be compared between treatment arms.

• Final treatment outcome at the end of treatment according to WHO definitions of cure will be compared between treatment arms.

• Two and three months culture conversion rates will be compared between treatment arms.

• Steady-state plasma pharmacokinetic parameters will be compared between treatment arms.

Study description

Background summary

Each year approximately 10 million people get sick of tuberculosis and in 2020 1.3 million people died due to TB. This disease remains the deadliest infectious disease in the world regardless of its cheap treatment and high cure rates. Treatment for drug-susceptible TB consists of 2 months intensive treatment with isoniazid, rifampicin, ethambutol and pyrazinamide, and thereafter a continuation phase of 4 months with isoniazid and rifampicin

according to guidelines. Current treatment for drug-susceptible TB has to be given for at least 6 months, which is long. It can lead to side-effects, which can decrease medication adherence. The current TB treatment is suboptimal, leading to favourable treatment outcomes in only 80% of the patients under programmatic circumstances.
Drug resistance to the key first-line drugs rifampicin and isoniazid is increasing. The aim of the WHO *End TB Strategy* is to end the global TB pandemic by 2035. This ambitious goal is dependent on the achievement in several areas before the year 2025: vaccines, new drugs and optimization of standard drugs and point-of-care diagnostic tests. Rifampicin, a drug with a well-known safety profile and efficacy data is currently dosed sub-optimal. The dose was selected when introduced in the 1970s because of financial reasons, fear for toxicity and because serum concentrations were well above the MIC.

There is substantial increasing evidence that higher doses of rifampicin are more optimal in terms of efficacy, prevention of resistance and are better tolerated than expected. The simple intervention to increase the dose and induce better outcome, reduce resistance selection and shorten treatment can have a major impact, contributing to WHO end TB strategy.

Study objective

This study has been transitioned to CTIS with ID 2023-509885-39-00 check the CTIS register for the current data.

The primary objective is to describe and compare the incidence of hepatotoxicity in standard care and in a regimen with an optimized dose of 1800 mg rifampicin in patients with rifampicin-susceptible tuberculosis. We identified hypotheses for non-inferiority. The null hypothesis states that the regimen with the optimized dose of rifampicin shows more hepatotoxicity than the regimen with the standard rifampicin dose. The alternative hypothesis states that there is no clinically relevant difference in hepatotoxicity between the regimen with an optimized dose of rifampicin and the regimen with the standard dose. In this case, the regimen with an optimized dose is non-inferior to the regimen with a standard dose of rifampicin.

The secondary objectives are:
• To compare any adverse events in the optimized dose regimen versus the standard dose regimen.
• To compare final treatment outcome at the end of treatment according to WHO definitions of cure in the optimized dose regimen versus the standard dose regimen.
• To compare two and three months culture conversion rates in the optimized dose regimen versus the standard dose regimen.
• To describe and compare the steady-state plasma pharmacokinetics of the optimized dose regimen versus the standard dose regimen. This will be performed

depending on the availability of pharmacological analyses.

Study design

This is a pragmatic randomized controlled open label non-inferiority phase III trial, with balanced 1:1 stratified randomization.

Intervention

We will compare a regimen with an optimized dose of rifampicin, to the standard regimen, as described below:
• Experimental arm with daily 1800 mg rifampicin for 6 months: 2HR1800ZE/4HR1800
• Control arm with the daily standard regimen for 6 months: 2HRZE/4HR

Study burden and risks

As this is a pragmatic trial, which is performed as much as possible within local standard of care, we expect there not to be much additional burden for participants. The planned study visits (wk1, wk2, wk4, wk6, wk8, wk 12, wk 17, wk 22 and wk 26) are adapted to the standard of care. Lab assessments, which include blood samples, have to be performed four times during the study period. The MAMS study of our group showed that a rifampicin dose of 35 mg/kg per day for 12 weeks was safe. In the PanACEA HIGHRIF1 study higher doses up to 40 mg rifampicin/kg were well tolerated for 7 days with monotherapy and additionally 7 days with combination therapy. However, we give a lower dose of rifampicin in the experimental arm, as 1800 mg is closest to a dose of 35 mg/kg. According to a retrospective cohort study a higher dose of rifampicin was safe and well-tolerated in patients with severe disease and/or low rifampicin plasma concentrations at the beginning. We have not seen flu-like syndrome in any of our high dose rifampicin studies and no higher incidence of hepatotoxicity was seen in our studies with pulmonary TB with higher doses of rifampicin up to 35 mg/kg.

Contacts

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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 patient has a diagnosis of pulmonary tuberculosis according to the local diagnostic criteria.
The patient is aged 18 years or older at the day of informed consent.
No known allergic reactions or toxicity to rifampicin in the past.

Exclusion criteria

Patient infected with a rifampicin-resistant strain of M. tuberculosis.
The patient has TB meningitis.
The patient is in a coma.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel

Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	15-01-2024
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	rifampicin
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	11-04-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	03-08-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-04-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	05-05-2023
Application type:	Amendment

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
EU-CTR	CTIS2023-509885-39-00
EudraCT	EUCTR2022-000632-27-NL
CCMO	NL80680.091.22