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Rifampin versus isoniazid for the treatment of latent tuberculosis infection: Part 3 effectiveness

Submission date
02/04/2009

Recruitment status
No longer recruiting

Registration date
29/05/2009

Overall study status
Completed

Last Edited
22/02/2019

Condition category
Infections and Infestations

[X] Prospectively registered

[_] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
On a global scale, tuberculosis (TB) is the single most important infectious cause of illness and death. The World Health Organization has estimated that one-third of the entire worlds population carries the bacterium that causes TB (i.e. they have latent TB infection). Of these, 8 million people develop active TB and almost 2 million die each year. This occurs mostly in disadvantaged populations. A key TB control strategy is to treat people who have latent TB infection (LTBI) to prevent them from developing active TB. The current standard treatment for LTBI is to take Isoniazid for 9 months (9INH). This treatment works very well if taken regularly. Serious side effects such as injury to the liver can occur. A recommended alternative to 9INH is Rifampin treatment for 4 months (4RIF). Based on some research on the treatment of LTBI, and extrapolating from extensive experience with treatment of active TB, it is believed that 4RIF will work as well as 9INH. The goal of this research study is to compare 9INH to 4RIF for the treatment of LTBI. The main goal of the study is to compare the number of study subjects that develop active TB between the two treatment groups.

Who can participate?
Adults (aged over 18, either sex) diagnosed with latent TB infection.

What does the study involve?
Eligible subjects will provide written consent and then be randomly divided in equal numbers to receive the treatment of either 9INH or 4RIF. Subjects will then be followed by their usual healthcare providers during treatment and then contacted every 3 months until the end of the study (28 months after starting the study). We will also compare compliance (i.e. taking all the treatment properly), safety and costs between the two groups.

What are the possible benefits and risks of participating?
Side effects common to both Isoniazid and Rifampin include digestive problems (abdominal cramps, hepato-toxicity, loss of appetite, nausea, vomiting), allergic reactions (itchiness, rash, redness), and lack of energy and fatigue. Less than 5% of the participants are expected to experience these side effects. Side effects associated with the use of Rifampin include orange

secretions (tears, urine) and a decrease in how well hormonal birth control methods work. Side effects associated with the use of Isoniazid include sensations of burning, numbness, or tingling in the extremities (hands and feet). All participants will be carefully monitored for any side effects and treated appropriately. No financial compensation will be given for participation in the study.

Where is the study run from?
Recruitment will be conducted in specialised clinics that treat lung disease in Australia, Benin, Brazil, Canada, Ghana, Guinea, Indonesia, South Korea, and Saudi Arabia. The coordinating centre is located in Montreal, Canada, at the Montreal Chest Institute (McGill University Health Centre).

When is the study starting and how long is it expected to run for?
The study began in 2009, recruitment will end in 2013, and the study is expected to finish in 2016.

Who is funding the study?
This research program is funded by the Canadian Institute of Health Research (CIHR).

Who is the main contact?
Dr Dick Menzies
Dick.Menzies@mcgill.ca

Contact information

Type(s)
Scientific

Contact name
Dr Dick Menzies

Contact details
Montreal Chest Institute
3650 St-Urbain, room K.124
Montreal, Quebec
Canada
H2X 2P4

Type(s)
Scientific

Contact name
Ms Chantal Valiquette

Contact details
MUHC, Montreal Chest Institute
3650 St-Urbain, room K 3.02
Montreal
Canada
H2X 2P4

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT00931736

Secondary identifying numbers
MCT-94831

Study information

Scientific Title
A randomised clinical trial comparing 4 months of rifampin to 9 months of isoniazid for the treatment of latent tuberculosis infection: Part 3 effectiveness

Acronym
RCT Phase 3

Study objectives
Therapy of latent tuberculosis infection (LTBI) with four months of daily rifampin (4RIF) will result in cumulative incidence of microbiologically-confirmed active tuberculosis (TB) during 28 months following randomisation, that is significantly lower than the cumulative incidence of active TB among participants randomised to nine months of daily isoniazid (9INH).

As of 11/09/2009 this record was updated to include an actual start date of 04/08/2009. The initial anticipated start date was 15/07/2009.

As of 31/08/2010 this record was updated; any changes can be found in the relevant field with the above update date. Please note that at this time, Guinea was removed from the countries of recruitment list, and Ghana and Indonesia were added.

As of 26/07/2012 this record was updated; any change can be found in the relevant field with the above update date. Please note that Guinea was added to the countries of recruitment list.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. McGill University Health Centre (Centre universitaire de sante McGill) Biomedical-C Research Ethics Board approved 08/06/2009 (ref: #BMC-09-007)
2. Version 2 of protocol approved 27/01/2010, annual renewal of protocol approved on 23/04 /2010
3. Version 6 of protocol approved 12/07/2011, annual renewal of protocol approved on 03/05 /2012 (Version 3 of protocol approved on 12/05/2010; Version 4 of protocol approved on 08/02 /2011; Version 5 of protocol approved 13/06/2011)

Study design

Multicentre randomised two-arm positive controlled open-labelled clinical trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Latent tuberculosis infection

Interventions
Amended as of 12/06/2009:
Rifampin (drug) and isoniazid (drug). The dosage of the medication is determined according to the weight of the subject:
Isoniazid: once per day, in pill format, for a total daily dose of 300 mg if subject weighs greater than or equal to 42 kg, otherwise 200 mg. Total duration of treatment is for 9 months.
Rifampin: once per day, in pill format, for a total daily dose of 600 mg if the subject weighs greater than or equal to 50 kg, 450 mg if the subject weighs greater than or equal to 36 kg and less than 50 kg, otherwise 300 mg for those weighing less than 36 kg. Total duration of treatment is for 4 months.
Both arms of the trial will be followed for 28 months post-randomisation.

Initial information at time of registration:
Rifampin (drug) and isoniazid (drug). The dosage of the medication is determined according to the weight of the subject:
Isoniazid: once per day, in pill format, for a total daily dose of 300 mg if subject weighs greater than or equal to 42 kg, otherwise 200 mg. Total duration of treatment is for 9 months.
Rifampin: once per day, in pill format, for a total daily dose of 600 mg if the subject weighs greater than or equal to 50 kg, 450 mg if the subject weighs greater than or equal to 40 kg and less than 50 kg, otherwise 300 mg for those weighing less than 40 kg. Total duration of treatment is for 4 months.
Both arms of the trial will be followed for 28 months post-randomisation.

Intervention Type
Drug

Drug/device/biological/vaccine name(s)
Rifampin, isoniazid

Primary outcome measure

To compare the cumulative incidence during 28 months after randomisation, of confirmed active tuberculosis (TB) among all persons randomised (effectiveness, using intention to treat analysis) to 4RIF and 9INH

Secondary outcome measures
Current secondary outcome measures as of 26/07/2012:
1. Compare the cumulative incidence of confirmed active TB among those who took at least 80% of doses of the LTBI treatment to which they were randomized, in less than 120% of the allowed time (i.e. efficacy).
2. Compare the cumulative incidence of probable, as well as confirmed active TB between patients randomized to the two regimens during 28 months following randomization.
3. Compare rates of Grades 3&4 adverse events during treatment between subjects randomized to the two regimens.
4. Compare health system costs, and cost-effectiveness of the two regimens, in the different sites.
5. Describe occurrence of drug resistance (to INH or RIF) among subjects who develop confirmed active TB.

Previous secondary outcome measures until 26/07/2012:
Compare the cumulative incidence of confirmed active TB among those who took at least 80% of doses of the LTBI treatment to which they were randomised, in less than 120% of the allowed time (i.e. efficacy)

Overall study start date
04/08/2009

Completion date
31/03/2016

Eligibility

Key inclusion criteria
Current information as of 31/08/2010:
Adults (aged greater than 18 years, either sex) with documented positive tuberculin skin test (TST) (or in the absence of a TST, a documented positive Quantiferon test [QFT]) and prescribed 9INH for LTBI, following authoritative recommendations.

Initial information at time of registration:
Adults (aged greater than 18 years, either sex) with documented positive tuberculin skin test (TST) and prescribed 9INH for LTBI, following authoritative recommendations.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex

Both

Target number of participants
5720

Key exclusion criteria
1. Patients who were contacts of TB cases known to be resistant to INH, RIF, or both (i.e. multi-drug resistant [MDR])
2. Known human immunodeficiency virus (HIV)-infected individuals on anti-retroviral agents whose efficacy would be substantially reduced by rifampin, unless therapy can safely be changed to agents not affected by rifampin
3. Pregnant women - rifampin and INH are considered safe in pregnancy, but therapy is usually deferred until 2 - 3 months post-partum to avoid foetal risk and the potential for increased hepato-toxicity immediately post-partum
4. Patient on any medication with clinically important drug interactions with INH or RIF, which their physician believes would make either arm contra-indicated
5. History of allergy/hypersensitivity to INH or to rifampin, rifabutin or rifapentine
6. Active TB. Patients initially suspected to have active TB can be randomised once this has been excluded.
7. Persons who have already started LTBI therapy

Date of first enrolment
04/08/2009

Date of final enrolment
31/12/2014

Locations

Countries of recruitment
Australia

Benin

Brazil

Canada

Ghana

Guinea

Indonesia

Korea, South

Saudi Arabia

Study participating centre

Montreal Chest Institute
Montreal, Quebec
Canada
H2X 2P4

Sponsor information

Organisation
The Research Institute of the McGill University Health Centre (Canada)

Sponsor details
c/o Vassilios Papadopoulos
Executive Director and Chief Scientific Officer
2155 Guy Street, Suite 500
Montreal QC
Canada
H3H 2R9

Sponsor type
Research organisation

Website
http://www.muhc.ca/research/

ROR
https://ror.org/04cpxjv19

Funder(s)

Funder type
Research organisation

Funder Name
Canadian Institutes of Health Research

Alternative Name(s)
Instituts de Recherche en Santé du Canada, Canadian Institutes of Health Research (CIHR), CIHR_IRSC, Canadian Institutes of Health Research | Ottawa ON, CIHR, IRSC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
Canada

Results and Publications

Publication and dissemination plan
To be confirmed at a later date

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	adverse events results	18/11/2008		Yes	No
Results article	results	02/08/2018	22/02/2019	Yes	No