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Intensified treatment for tuberculous meningitis to reduce mortality

Submission date
05/10/2009

Recruitment status
No longer recruiting

Registration date
06/10/2009

Overall study status
Completed

Last Edited
28/10/2020

Condition category
Infections and Infestations

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Infection with bacteria called M. tuberculosis causes tuberculosis and is generally treated with a course of four or five types of antibiotic drugs. In cases of tuberculous meningitis (TBM), the bacteria has gotten into a patient's brain and spinal cord, causing life-threatening inflammation. It is estimated that almost one third of patients with TBM die, despite treatment. HIV patients have a worse prognosis - about two thirds of patients with both TBM and HIV die. Without treatment all patients with TBM die. The investigators of this study believe that the usual course of antibiotic drugs often does not work as well for TBM as for tuberculosis of the lungs, because the drugs are not able to effectively penetrate to the patient's brain to treat the infection there. This study examines the effect of increased dosages and addition of drugs to the standard course of antibiotics for patients with TBM, in order to optimise the killing of bacteria in the brain.

Who can participate?
The study aims to recruit 750 patients with TBM to the study, including patients with HIV. Patients need to be over 18 years of age, have a clinical diagnosis of TBM, and give informed consent to participate.

What does the study involve?
Patients are randomly allocated to one of two treatment groups. The intensified treatment group receives the normal course of anti-tuberculosis treatment, plus levofloxacin and increased dosages of rifampicin. The standard treatment group receives the normal course of anti-tuberculosis treatment, plus placebo (dummy) pills that look the same as levofloxacin and rifampicin, but do not contain the actual drug. By giving one group placebo pills, neither the patient nor the doctor can know which group a patient belongs to. This is the best way to study the difference in outcome in the end. The patients are monitored daily for general health, drug side-effects and mental status. Blood and brain fluid (cerebrospinal fluid) testing is carried out on multiple occasions. Patients are monitored daily by a study doctor while in the hospital until they are discharged, generally after one month of treatment. When in hospital, blood will be drawn each week, or if the treating doctor thinks it is necessary it will be checked more often. They are then followed up each month at the outpatient department until the end of treatment at 9 total months or until the patient dies or withdraws from the study. Lumbar punctures

(taking fluid from the spine by a hollow needle in the lower back) will be carried out when admitted to hospital and after 1, 2 and 9 months, in order to see if the infection is clearing. If the treating doctor thinks it is necessary they may be done more often. As per hospital procedure, patients may object to the procedure - this will not influence their treatment.

What are the possible benefits and risks of participating?
These drugs are generally known to be safe. There is a lot of information about side affects of these drugs in patients with tuberculosis or with other infections and in general the side effects are mild. The most common side effects are abdominal (stomach) problems, such as vomiting or diarrhoea and inflammation of the liver for rifampicin. Levofloxacin is also well tolerated, but can cause abdominal problems, headache and dizziness and in very rare cases inflammation of tendons and cardiac problems. Some patients with cardiac problems in the past may be at greater risk for developing cardiac side effects, so all patients in the study will get an ECG done on separate occasions to check whether it is safe to give this drug and whether problems develop during treatment. The treatment and tests during the study period will be paid for by the study team. For poor patients this may be a benefit of being in the study.

Where is the study run from?
This study is run by researchers at the Oxford University Clinical Research Unit in Vietnam, in partnership with the Hospital for Tropical Diseases and Pham Ngoc Thach Hospital in Ho Chi Minh City, the two study sites.

When is the study starting and how long is it expected to run for?
The study began in April 2011 and is expected to finish in March 2015.

Who is funding the study?
The Wellcome Trust (UK).

Who is the main contact?
Clinical Trials Unit at the Oxford University Clinical Research Unit in Vietnam
Tel: +84 839 241 983

Contact information

Type(s)
Scientific

Contact name
Dr Laura Merson

Contact details
Hospital for Tropical Diseases
Wellcome Trust Major Overseas Programme
Oxford University Clinical Research Unit
190 Ben Ham Tu, District 5
Ho Chi Minh City
Viet Nam
-
+84 (0)8 923 7954
lmerson@oucru.org

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
OXTREC No 33/09; 084253

Study information

Scientific Title
A randomised, double-blind, placebo-controlled trial to investigate the effect of intensified treatment with high dose rifampicin and levofloxacin for adult patients with tuberculous meningitis

Acronym
05TB

Study objectives
Intensifying the induction phase of treatment of tuberculous (TB) meningitis will result in reduced mortality.

On 24/02/2011 the anticipated start and end dates for this trial were updated:
1. The overall trial start date was changed from 01/01/2010 to 01/04/2011.
2. The overall trial end date was changed from 01/12/2012 to 01/12/2013.

On 14/11/2013 the overall trial end date was changed from 01/12/2013 to 01/05/2015.

On 25/07/2014 the following changes were made to the trial record:
1. The overall trial start date was changed from 01/04/2011 to 18/04/2011.
2. The overall trial end date was changed from 01/05/2015 to 15/03/2015.
3. The target number of participants was changed from '750' to '750 with at least 350 HIV-positive participants. Enrollment completed; final enrollment 817'.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Oxford Tropical Medicine Research Ethics Committee (OXTREC) (UK), 11/08/2009, ref: 33/09
2. Research Ethics Board of the Hospital for Tropical Diseases, Ho Chi Minh City (Vietnam), 09/09/2010
3. Research Ethics Board of the Pham Ngoc Thach Hospital, Ho Chi Minh City (Vietnam), 28/04/2010

Study design
Randomised double-blind placebo-controlled 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
Tuberculous meningitis

Interventions
Patients will be randomised to one of two treatment groups:
Group A: Rifampicin 15 mg/kg/day, levofloxacin 20 mg/kg/day, isonazid 5 mg/kg once daily (od) orally (po) (maximum of 300 mg/day), pyrazinamide 25 mg/kg od po (maximum of 2 g/day) and ethambutol 20 mg/kg od po (maximum of 1.2 g/day) or streptomycin 20 mg/kg od intramuscularly (im) (maximum of 1 g/day) for two months followed by standard therapy for 8.5 months
Group B: Rifampcin 10 mg/kg/day, placebo, isonazid 5 mg/kg od po (maximum of 300 mg/day), pyrazinamide 25 mg/kg od po (maximum of 2 g/day) and ethambutol 20 mg/kg od po (maximum of 1.2 g/day) or streptomycin 20 mg/kg od im (maximum of 1 g/day) for two months followed by standard therapy for 8.5 months

Standard therapy is according to the Vietnam National Tuberculous Programme guidelines. After the first two months detailed above, patients will be treated with rifampicin 10 mg/kg od po, isonazid 5 mg/kg od po (maximum of 300 mg/day), pyrazinamide 25 mg/kg od po (maximum of 2 g/day) and ethambutol 20 mg/kg od po (maximum of 1.2 g/day) or streptomycin 20 mg/kg od im (maximum of 1 g/day) for 2.5 months, followed by 6 months of rifampcin 10 mg/kg od po and isonazid 5 mg/kg od po (maximum of 300 mg/day).

Patients will also be treated as per clinical care guidelines with dexamethasone at enrolment and anti-retrovirals for human immunodeficiency virus (HIV) positive patients.

Intervention Type
Drug

Phase
Phase IV

Drug/device/biological/vaccine name(s)
Rifampicin, levofloxacin, isonazid, pyrazinamide, ethambutol, streptomycin

Primary outcome measure

Overall survival during a follow-up period of 9 months

Secondary outcome measures
1. Neurological disability at 9 months as assessed using the 'simple questions' and Rankin score
2. Time to new neurological event. Neurological events are defined as:
2.1. Any of the following adverse events: cerebellar symptoms, coma, hemiplegia, neurological deteoriation, paraplegia, seizures, cerebral herniation or cranial nerve palsy
2.2. A fall in Glasgow Coma Score by greater than or equal to 2 points for greater than or equal to 2 days from highest previously recorded Glasgow Coma Score (including baseline)
3. Any grade 3 or 4 adverse event
4. Rate of treatment interruption for adverse events
5. The rates of asymptomatic transaminitis and symptomatic hepatitis
6. Time to new or recurrent acquired immune deficiency syndrome (AIDS) defining illness or death (in HIV-positive patients only)
7. Time to undetectable viral load, CD4 count at end of therapy (in HIV-positive patients only)

Overall study start date
18/04/2011

Completion date
15/03/2015

Eligibility

Key inclusion criteria
Greater or equal to 15 years of age (either sex) with a clinical diagnosis of tuberculous meningitis

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
750 with at least 350 HIV-positive participants. Enrollment completed; final enrollment 817

Key exclusion criteria
1. Positive cerebrospinal fluid (CSF) Gram or India Ink stain
2. Known or suspected pregnancy
3. Known hypersensitivity/intolerance to fluoroquinolones or rifampicin
4. Estimated glomerular filtration rate (GFR) less than 40 ml/min
5. Laboratory contraindications to antituberculous therapy:
5.1. Bilirubin greater than 2.5 x upper limit of normal (ULN)
5.2. Aspartate aminotransferase (AST) or alanine aminotransferase (ALT) greater than 5 x ULN
6. Lack of consent

Date of first enrolment

18/04/2011

Date of final enrolment
18/06/2014

Locations

Countries of recruitment
Viet Nam

Study participating centre
Hospital for Tropical Diseases
Ho Chi Minh City
Viet Nam
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Sponsor information

Organisation
University of Oxford (UK)

Sponsor details
Centre of Clinical Vaccinology and Tropical Medicine (CCVTM)
Churchill Hospital
Old Road
Oxford
England
United Kingdom
OX3 7LJ

Sponsor type
University/education

Website
http://www.ox.ac.uk/

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	02/02/2011		Yes	No
Protocol article	protocol	02/02/2011		Yes	No
Results article	results	14/01/2016		Yes	No
Results article	results	01/04/2020	28/10/2020	Yes	No