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Adjunctive dexamethasone in HIV-infected adults with cryptococcal meningitis

Submission date
13/07/2012

Recruitment status
No longer recruiting

Registration date
26/07/2012

Overall study status
Completed

Last Edited
26/02/2016

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
Cryptococcal meningitis (CM) causes around 625,000 deaths every year, most of which occur within 3 months of diagnosis. It is the leading cause of death in HIV patients in Asia and Africa. The incidence in these regions is the highest in the world - in Africa, it is estimated there are more deaths due to CM than due to tuberculosis. There has been no major advance in the treatment of CM since the 1970s. The main drugs used to treat CM (amphotericin B and flucytosine) are over 50 years old, and they are often poorly available where the disease burden is highest. While effective antifungal therapy is key, adjunctive treatments, which have been seen to have dramatic effects on death rates in other nervous system infections, are untested in CM. Given the high death rates in patients receiving the best current treatment and the lack of new drugs on the horizon, adjuvant treatments offer the greatest potential to reduce death rates in CM. Dexamethasone is a cheap, readily available and practical treatment. This study aims to find out whether adding dexamethasone to standard antifungal therapy reduces death rates in CM.

Who can participate?
Patients who are more than 18 years of age, HIV-positive and have CM can participate in the study.

What does the study involve?
Eligible participants will randomly be allocated to one of two groups: the dexamethasone group or the dummy drug (placebo) group. The dexamethasone dose will depend on the participants body weight and the dose will be reduced each week. All patients will also receive antifungal treatment consisting of 2 weeks of amphotericin B combined with high-dose fluconazole, followed by fluconazole alone for 8 weeks (10 weeks in total). Patients will be in hospital for at least 2 weeks and then followed-up until week 10 and if possible to 6 months.

What are the possible benefits and risks of participating?
It is unknown if the participants in the dexamethasone group will benefit from the treatment. The additional monitoring and follow-up of patients by dedicated study staff may be of benefit to patients treated in resource-limited settings. The study results will help us to understand how to best treat CM and it may help others with this disease in the future. This study will use a drug

that has been studied thoroughly and its toxicities are well known. Blood and cerebral spinal fluid will be taken for research tests. These volumes have very little risk of affecting the participant's health. This procedure carries a small risk of bruising and infection. Dexamethasone may be suppress growth in children and fetuses. Therefore, children and pregnant women have been excluded from this study.

Where is the study run from?
Vietnam, Indonesia, Thailand, Laos, Uganda and Malawi

When is the study starting and how long is it expected to run for?
It started in September 2012 and it should run for about three years

Who is funding the study?
The Department for International Development, the Wellcome Trust and the Medical Research Council in the UK

Who is the main contact?
Dr Jeremy Day
jday@oucru.org

Study website
https://portal.oucru.org/RS/04CN%20%20CryptoDe/Forms/AllItems.aspx

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
04CN

Study information

Scientific Title
A randomized, double-blind, placebo-controlled phase III trial of adjunctive dexamethasone in HIV-infected adults with cryptococcal meningitis (CRYPTODEX)

Acronym
CRYPTODEX

Study objectives
Dexamethasone used as adjunctive therapy may improve the 10-week survival in adult HIV-infected patients with cryptococcal meningitis.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Oxford Tropical Research Ethics Committee, 13/06/2012, ref: 25-12

Study design
Randomized double-blind placebo-controlled trial with two parallel arms

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

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
Cryptococcus meningitis/HIV

Interventions
Eligible participants will randomly be allocated to either dexamethasone or placebo group.

Dexamethasone will be given in a reducing dose according to body weight.
This dose is identical to the dose used in patients with Grade 1 tuberculous meningitis and has been shown to have a low rate of side effects. Dexamethasone/placebo will be administered

intravenously while the antifungal treatment is intravenous, and orally once antifungal treatment is administered orally. Treatment will be weight-dosed to the nearest half milligram. With the exception of the first dose, which should be given with the first dose of anti-fungal therapy, dexamethasone should be given in the morning.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Dexamethasone

Primary outcome measure
Overall survival until 10 weeks after randomisation

Secondary outcome measures
1. Survival until 6 months after randomization
2. Disability at 10 weeks and 6 months
3. Rate of CSF sterilisation during the first 2 weeks
4. Adverse events
5. Rate of IRIS until 10 weeks
6. Time to new AIDS-defining illnesses or death until 10 weeks
7. Visual deficit at 10 weeks
8. Time to new neurological event or death until 10 weeks
9. Longitudinal measurements of intracranial pressure during the first 2 weeks
10. Antifungal treatment intensification or re-treatment for cryptococcal meningitis in the 6 months post randomisation

Overall study start date
30/09/2012

Completion date
30/12/2015

Eligibility

Key inclusion criteria
1. Age >18 years
2. HIV antibody positive
3. Cryptococcal meningitis defined as a syndrome consistent with CM and one or more of:
3.1. Positive CSF India ink (budding encapsulated yeasts)
3.2. C. neoformans cultured from CSF or blood
3.3. Positive cryptococcal antigen Lateral Flow Antigen Test (LFA) in CSF
4. Informed consent to participate given by patient or acceptable representative

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
880

Key exclusion criteria
Current exclusion criteria as of 23/09/2014:
1. Pregnancy
2. Active gastrointestinal bleeding (defined as vomiting blood or malaena stool in the previous week)
3. Currently receiving treatment for cryptococcal meningitis and having received > 1 week of anti-cryptococcal meningitis therapy
4. Known allergy to dexamethasone
5. Current steroid use defined as:
5.1. Currently receiving the equivalent of prednisolone 40 mg/day or more
5.2. Currently receiving steroid therapy (any dose) for more than 3 weeks (except topical steroids which are permitted)
6. Concurrent condition for which corticosteroids are indicated because of proven benefit (such as severe Pneumocystis pneumonia [pO2<70 mmHg] or tuberculous meningitis)
7. Renal failure (defined as creatinine >3*ULN, despite adequate hydration)

Previous exclusion criteria:
1. Pregnancy
2. Active gastrointestinal bleeding (defined as vomiting blood or malaena stool in the previous week)
3. Currently receiving treatment for cryptococcal meningitis and having received > 1 week of anti-cryptococcal meningitis therapy
4. Known allergy to dexamethasone
5. Current steroid use defined as:
5.1. Currently receiving the equivalent of prednisolone 40 mg/day or more
5.2. Currently receiving steroid therapy (any dose) for more than 3 weeks (except topical steroids which are permitted)
6. Renal failure (defined as creatinine >3*ULN, despite adequate hydration)

Date of first enrolment
19/02/2013

Date of final enrolment
29/08/2014

Locations

Countries of recruitment

Indonesia

Lao People's Democratic Republic

Malawi

Thailand

Uganda

Viet Nam

Study participating centre
Oxford University Clinical Research Unit
Ho Chi Minh
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Sponsor information

Organisation
University of Oxford (UK)

Sponsor details
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Sponsor type
University/education

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

ROR
https://ror.org/052gg0110

Funder(s)

Funder type
Charity

Funder Name
Department for International Development

Alternative Name(s)
Department for International Development, UK, DFID

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
Wellcome Trust

Alternative Name(s)

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
United Kingdom

Funder Name
Medical Research Council (UK), ref: G1100684/1

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype

National government

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	12/11/2014		Yes	No
Results article	results	11/02/2016		Yes	No