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Clinical study comparing the nifurtimox-eflornithine combination with the standard eflornithine regimen for the treatment of Trypanosoma brucei gambiense human African trypanosomiasis in the meningo-encephalitic phase

Submission date	Recruitment status	[_] Prospectively registered
12/09/2005	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
18/04/2008	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
28/11/2018	Infections and Infestations	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

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Additional identifiers

Protocol serial number
WHO ref: A50402 and A60444; NFE0105; NFE0206

Study information

Scientific Title
Clinical study comparing the nifurtimox-eflornithine combination with the standard eflornithine regimen for the treatment of Trypanosoma brucei gambiense human African trypanosomiasis in the meningo-encephalitic phase

Study objectives
Melarsoprol is the most commonly used product for the treatment of patients suffering from human African trypanosomiasis (HAT) in the meningo-encephalitic (second, late) phase. This treatment is frequently complicated by fatal reactive encephalopathy, and at the same time resistance is beginning to appear in various countries. Eflornithine is effective and better tolerated, but it is more difficult to use. Nifurtimox, registered in several South American countries for treatment of Chagas' disease but used off label since the 1970's in series of cases of meningo-encephalitic HAT, is at present the only other potential alternative for the treatment of late-stage HAT.

The very limited number of compounds available, the lack of prospects for the development of new products and the emergence of resistance are arguments for the use of therapeutic combinations. Ideally, drug combinations should allow for reductions in the dosages of the drugs used in a way that, in particular in the case of toxic drugs such as those used for second stage HAT, the toxicity of the combination does not exceed that of either monotherapy. Of the three drug combinations nowadays possible: melarsoprol-nifurtimox, melarsoprol-eflornithine and eflornithine-nifurtimox, the last one has (in two different dosing regimens) shown the least treatment-associated toxicity and mortality in the 69 patients treated in one previous and this clinical trial to date. Good tolerability was also observed in a case series of 31 patients. The efficacy data to date suggest that efficacy is comparable to that of eflornithine and that of melarsoprol (in areas without high melarsoprol failure rates).

The main objective of the study is to compare the therapeutic combination of intravenous (IV) eflornithine and oral nifurtimox to the standard IV eflornithine regimen in terms of therapeutic efficacy and clinical safety, in patients suffering from Trypanosoma brucei gambiense (Tbg) HAT in the meningo-encephalitic phase. If therapeutic non-inferiority is shown, the combination regimen will represent an alternative therapy with simpler and shorter administration regimen, shorter hospitalisation, lower cost and some level of protection against the emergence of resistance.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics approval received from:
1. Ethical Clearance Committee (Uganda) on the 8th May 2005 and 8th May 2006 (ref: VCD/UNCT /06)
2. World Health Organization (WHO) Ethics Review Committee (ERC) on the 30th May 2005, and was reviewed on the 26th April 2006 and 27th February 2007

Study design
Randomised, open label, clinical non-inferiority trial

Primary study design

Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Human African trypanosomiasis

Interventions
1. Eflornithine IV 7 days 400 mg/kg/day 12 hourly and nifurtimox orally 10 days 15 mg/kg/day 8 hourly
2. Eflornithine IV 14 days 400 mg/kg/day 6 hourly

The total duration of follow up is 18 months for both arms.

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Intervention Type
Drug

Phase
Not Specified

Drug/device/biological/vaccine name(s)
Eflornithine, nifurtimox

Primary outcome(s)
The cure rate assessed via the number of alive subjects 18 months after treatment without laboratory signs of infection, i.e. absence of trypanosome(s) in the CSF, blood or lymph node fluid and CSF leukocytes count less than 20/µl.

Key secondary outcome(s)
1. The duration of survival without laboratory signs of infection up to 18 months after treatment
2. Proportion of serious adverse events and of major (grade 3 and 4) adverse events related to the treatment (adverse occurring in each treatment arm)

Completion date
13/06/2009

Eligibility

Key inclusion criteria
1. Confirmed second-stage Tb gambiense infection: presence of the parasite in blood, lymph node fluid or cerebrospinal fluid (CSF) and greater than 20 white blood cells/µL in CSF
2. Age 15 years or older, either sex
3. Resident in a radius of 50 km from Omugo Sleeping Sickness Treatment Centre
4. Written informed consent of the patient or of a legally acceptable representative if the patient is a minor (less than 18 years for both genders in Uganda) or unable to communicate

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
1. Pregnant woman (systematic testing (urine human chorionic gonadotropin [HCG]) of women of childbearing potential)
2. Treated for late-stage HAT during the last 36 months. Patients previously treated for first-stage (pentamidine) can be included.
3. Unlikely to have access to the treatment centre or be accessible at their place of residence for 18 months after treatment
4. Unable to take oral medication
5. Suffering from conditions other than second stage HAT that seriously limit the chances of survival over 18 months time
6. Severe anaemia (haemoglobin [Hb] less than 5 g/dl)
7. Severe underlying diseases upon admission (e.g. active tuberculosis and/or being treated for TB; bacterial or cryptoccocal meningitis; stages 3 or 4 human immunodeficiency virus [HIV] /acquired immune deficiency syndrome [AIDS] according to the WHO clinical definition) (WHO, 1986)
8. Renal failure based on clinical examination combined with biochemistry. Calculated creatinine clearance less than 20 mL/min (Cockcroft's equation).
8.1. Males: creatinine clearance (mL/min) = (Wt [kg] x 140 - age [years]) ÷ (72 x serum creatinine [mg/dL])
8.2. Females: 0.85 x the above value
9. Hepatic failure based on clinical examination combined with biochemistry total bilirubin greater than 50 µmol/L, alanine aminotransferase (ALAT)/glutamate pyruvate transaminase [GPT] greater than 70 UI/L

Date of first enrolment

01/11/2005

Date of final enrolment
13/06/2009

Locations

Countries of recruitment
Switzerland

Uganda

Study participating centre
World Health Organization (WHO)
Geneva-27
Switzerland
CH-1211

Sponsor information

Organisation
UNICEF/UNDP/World Bank/WHO Special Programme for Research and Training in Tropical Diseases (TDR)

ROR
https://ror.org/01f80g185

Funder(s)

Funder type
Research organisation

Funder Name
United Nations Children's Fund (UNICEF)/United Nations Development Programme (UNDP)/World Bank/World Health Organization (WHO) - Special Programme for Research and Training in Tropical Diseases (TDR)

Results and Publications

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?
Results article	results	22/02/2018		Yes	No