ISRCTN06010453 https://doi.org/10.1186/ISRCTN06010453

Comparison of doxycycline, minocycline, doxycycline plus albendazole and albendazole alone in their efficacy against onchocerciasis

Submission date
09/01/2012

Recruitment status
No longer recruiting

Registration date
20/02/2012

Overall study status
Completed

Last Edited
18/01/2019

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Onchocerciasis affects up to 37 million people worldwide and is most abundant in Africa. It is responsible for skin disease and blindness and is caused by a large worm (known as Onchocerca volvulus) which is transmitted in larval stage to humans via black flies which breed in rivers and streams - hence the name river blindness. When an infected black fly bites, infective larvae crawl into the bite wound. These migrate through the skin tissue and mature into adult worms located under the skin in self-contained nodules (onchocercomata) where they produce new larvae (microfilariae). Symptoms occur when microfilariae die in the skin. This can cause intense itching, skin inflammation and depigmentation. If the larvae migrate to the eye their death results in inflammation leading ultimately to blindness. Onchocerca volvulus has a unique feature shared with some other closely related worm species: it lives in a symbiosis with mutual benefit with bacteria named Wolbachia. These bacteria live inside the cells of the parasitic worms. Since the worms are dependent on Wolbachia bacteria for growth, development, reproduction and survival, eliminating the bacteria with antibiotic drugs kills the worms and delivers a new and practical solution for treatment of onchocerciasis. The currently shortest-known effective treatment to kill the worms is doxycycline 200 mg/ day given for 4 weeks. The aim of this study is to shorten the treatment period further and/or to find alternative treatments.

Who can participate?
Healthy adults (18-55 years) with at least one palpable nodule (onchocercoma).

What does the study involve?
Participants will be randomly allocated to receive one of the following five treatments:
1. Doxycycline 200 mg for 4 weeks
2. Minocycline 200 mg for 3 weeks
3. Doxycycline 200 mg for 3 weeks
4. Doxycycline 200 mg for 3 weeks plus albendazole 800mg for 3 days
5. Albendazole 800 mg for 3 days
The treatment will be administered on a daily basis by a trial clinician. Six months after treatment start all palpable nodules (onchocercomta) will be removed under local anaesthetic

and sterile conditions by an experienced surgeon in a hospital. After discharge from the hospital, wound dressing will be carried out by the research team until all wounds are healed. Before treatment and before removal of the nodules, little skin biopsies (skin-snips) will be taken to assess the number of larvae in the skin. Nodule sections will be analysed under the microscope to find out whether the drug regimens were effective in reducing the Wolbachia numbers in the worms and in damaging the worms. It is already known that effective antibiotic treatments reduce Wolbachia at least 10-fold and will have rendered the worms sterile at 6 months after treatment onset.

What are the possible benefits and risks of participating?
Benefits to the study participant include removal of onchocercomata, improvement of skin conditions such as papular dermatitis, improvement in general health, slight weight gain due to treatment of accompanying infections amenable by antibiotics, and free medical treatment for common illnesses during treatment period and follow-up. The risks to participants are adverse effects caused by the licensed study drugs and infection during operation, blood-sampling or skin snipping. All adverse effects caused by the study drugs or interventions will be treated and followed up by the research team until they are resolved.

Where is the study run from?
The treatment of the participants will be carried out in an area endemic for onchocerciasis in the western part of Ghana: Upper- and Lower Denkyira Districts, Dunkwa on Offin, Central Region; Amansie Central and Adanse South Districts, Ashanti Region).

When is the study starting and how long is it expected to run for?
The treatment of the participants will be carried out in January/February 2012.

Who is funding the study?
This study is funded by a grant from the Bill and Melinda Gates Foundation (USA) awarded to the Liverpool School of Tropical Medicine (UK).

Who is the main contact?
Prof. Dr. Achim Hoerauf
hoerauf@microbiology-bonn.de
Dr. Alexander Yaw Debrah
yadebrah@yahoo.com

Contact information

Type(s)
Scientific

Contact name
Prof Achim Hoerauf

Contact details
Institute for Medical Microbiology, Immunology and Parasitology (IMMIP)
University Clinic Bonn
Sigmund Freud Str.25
Bonn
Germany
53105

+49 (0) 228 287 15675
hoerauf@microbiology-bonn.de

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
Grant ref: 39284

Study information

Scientific Title
Comparison of doxycycline, minocycline, doxycycline plus albendazole and albendazole alone in their efficacy against onchocerciasis: a randomised open trial

Study objectives
To refine existing regimens of drugs with known activity against Wolbachia (doxycycline, minocycline):
1. To provide a shortened treatment period using minocycline 200 mg for 3 weeks, doxycycline 200 mg for 3 weeks or the combination of 3 weeks doxycycline 200 mg plus albendazole for 3 days.
2. To evaluate if treatment with above mentioned drug regimen shows equivalent Wolbachia reduction/blockage of embryogenesis after 6 months, compared to 4 weeks doxycycline 200 mg ('positive control').
3. To evaluate if treatment with above mentioned drug regimen shows superior Wolbachia reduction/blockage of embryogenesis after 6 months, compared to 3 days albendazole 800 mg ('negative control')

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Committee on Human Research Publication and Ethics, Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, 19/12/2011
2. Ethical Committee, University Clinic Bonn, 07/11/2011
3. Research Ethics Committee, Liverpool School of Tropical Medicine, 22/12/2011
The amendment for the follow-up 23 months after treatment onset was approved by all three Ethics Committees.

Study design
Randomised open trial pilot study

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
Onchocerciasis (Onchocerca volvulus)

Interventions
Treatment regimen 1 (n = 30): 4 weeks doxycycline 200 mg (2 capsules/day)
Treatment regimen 2 (n = 30): 3 weeks minocycline 200 mg (2 capsules/day)
Treatment regimen 3 (n = 30): 3 weeks doxycycline 200 mg (2 capsules/day)
Treatment regimen 4 (n = 30): 3 weeks doxycycline 200 mg (2 capsules/day) plus albendazole 800 mg (4 tablets/day) on day 9, 10 and 11 of treatment
Treatment regimen 5 (n = 30): 3 days albendazole 800 mg (4 tablets/day)

Volunteers for this study are recruited based on the inclusion and exclusion criteria and treated directly in their villages (Upper- and Lower Denkyira Districts, Dunkwa on Offin, Central Region; Amansie Central and Adanse South Districts, Ashanti Region). The study drugs will be distributed personally by the research staff and drug intake be monitored on a daily basis for 3 days up to 4 weeks depending on the regimen the participant is assigned to.

To assess the skin microfilarial load, skin biopsies are taken pre-treatment, as well as at 6 months after treatment (updated 27/10/2014: skin biopsies are taken pre-treatment, as well as at 6 and 23 months after treatment).

Nodulectomies to assess Wolbachia, worm vitality and embryogenesis will be performed 6 months after the start of drug administration. Onchocercomata will be removed under local anaesthesia in the hospital. Patients will be kept in hospital for the day of operation or one day longer (depending on the severity of operation) for observation before being discharged. Wound dressing will continue in the villages until all the wounds are healed.

Contact details for Joint Principal Investigator:
Dr Alexander Yaw Debrah
Kwame Nkrumah University of Science and Technology (KNUST), Kumasi Centre of Collaborative Research (KCCR)
University Post Office
Kumasi, Ghana
Tel: +233 51 60351
Fax: +233 51 62017
Email: yadebrah@yahoo.com

Intervention Type

Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Doxycycline, minocycline, albendazole

Primary outcome measure
Current primary outcome measures as of 27/10/2014:
Absence of Wolbachia endobacteria in adult worms assessed by immunohistology

Previous primary outcome measures:
Reduction of Wolbachia endobacteria in adult worms assessed by immunohistology 6 months after treatment onset

Secondary outcome measures
Current secondary outcome measures as of 27/10/2014:
1. Reduction of Wolbachia endobacteria in adult worms assessed by immunohistology 6 months after treatment onset
2. Reduction of Wolbachia endobacteria in adult worms assessed by PCR
3. Reduction of microfilariae in the skin (skin snips taken pre-treatment and after 6 as well as 23 months after treatment onset)
4. Absence of microfilariae in the skin (skin snips taken pre-treatment and after 6 as well as 23 months after treatment onset)
5. Evaluation of worm embryogenesis assessed by histology (6 months after treatment onset):
5.1. Normal embryos
5.2. Degenerated embryos
5.3. No embryos
6. Rates of nodules (onchocercomata) with microfilariae within the nodular tissue assessed by histology
7. Insemination of female worms assessed by histology 6 months after start of drug administration
8. Number of live/dead worms assessed by histology
9. Skin manifestation of the disease judged pre-treatment as well as 6 months after start of drug administration
10. Parasite-specific immunoglobulin subclasses and cytokine responses

Previous secondary outcome measures:
1. Absence of Wolbachia endobacteria adult worms assessed by immunohistology
2. Reduction of Wolbachia endobacteria in adult worms assessed by PCR
3. Reduction of microfilariae in the skin (skin snips taken pre-treatment and after 6 months)
4. Absence of microfilariae in the skin (skin snips taken pre-treatment and after 6 months)
5. Evaluation of worm embryogenesis assessed by histology (6 months after treatment onset):
5.1. Normal embryos
5.2. Degenerated embryos
5.3. No embryos
6. Parasite-specific immunoglobulin subclasses and cytokine responses

Overall study start date
10/01/2012

Completion date
30/06/2013

Eligibility

Key inclusion criteria
1. Participants of both sexes, between 18-55 years old
2. Presence of at least one onchocercoma detected by palpation
3. Participation in the Mass Drug Administration (MDA) depending on microfilaria (Mf) status:
3.1. Mf-positive (> 10 mf/mg skin) or > 2 palpable onchocercomata: no limitation of ivermectin (MDA) rounds
3.2. Mf-positive (0.1 - 10 mf/mg skin) and ≤ 2 palpable onchocercomata: last ivermectin treatment > 1 year ago and not more than three rounds
3.3. Mf-negative (0 mf/mg skin) ≤ 2 palpable onchocercomata: last ivermectin treatment > 1 year ago and not more than one round
4. Good general health without any clinical condition requiring long-term medication
5. Body weight > 40 kg
6. Willingness to participate in the study by signing the Infomed Consent Form (ICF)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Both

Target number of participants
150

Key exclusion criteria
1. Known intolerance to the study drugs (doxycycline, minocycline, albendazole)
2. Pregnancy (pregnancy tests will be carried out pre-treatment and 14 days after treatment onset)
3. Breastfeeding
4. History of severe allergic reaction or anaphylaxis
5. Alcohol or drug abuse
6. Evidence of clinically significant neurological, cardiac, pulmonary, hepatic or renal disease as far as can be assessed by history of participants, physical examination, and/or laboratory examinations (as specified under 10 and 11)
7. Behavioural, cognitive or psychiatric disease that in the opinion of the trial clinician affects the ability of the participant to understand and cooperate with the study protocol
8. Severe asthma (emergency room visit or hospitalization)

9. Participation in other drug trials while this study is ongoing
10. Laboratory evidence of liver disease (ALT, µGT greater than 1.5 times the upper limit of normal results as stated by the manufacturer, CHEM7®; ALT: (0 75 U/L), µGT: (females: 0 69.5 U /L; males: 0 80.7 U/L))
11. Laboratory evidence of renal disease (serum creatinine greater than 1.2 times the upper limit of normal results as stated by the manufacturer, CHEM7®; Crea: (0 1.8 mg/dL))
12. Any other condition that, in the opinion of the investigator (trial clinician), would risk the safety or rights of a participant in the trial or would render the subject unable to comply with the protocol

Date of first enrolment
10/01/2012

Date of final enrolment
30/06/2013

Locations

Countries of recruitment
Germany

Ghana

Study participating centre
Institute for Medical Microbiology, Immunology and Parasitology (IMMIP)
Bonn
Germany
53105

Sponsor information

Organisation
Liverpool School of Tropical Medicine (UK)

Sponsor details
c/o Prof Mark Taylor
Pembroke Place
Liverpool
England
United Kingdom
L3 5QA
+44 (0)151 705 3100
mark.taylor@liverpool.ac.uk

Sponsor type
University/education

Website
http://a-wol.com/

ROR
https://ror.org/03svjbs84

Funder(s)

Funder type
Charity

Funder Name
Bill and Melinda Gates Foundation (USA)

Alternative Name(s)
Bill & Melinda Gates Foundation, Gates Foundation, BMGF, B&MGF, GF

Funding Body Type
Government organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United States of America

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?
Results article	results	05/01/2017	18/01/2019	Yes	No