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The efficacy of rifapentine plus moxifloxacin against onchocerciasis: a randomized, open label pilot trial.

Submission date
04/04/2015

Recruitment status
No longer recruiting

Registration date
17/04/2015

Overall study status
Completed

Last Edited
05/12/2018

Condition category
Infections and Infestations

[X] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Plain English summary as of 05/12/2018:
Background and study aims
Onchocerciasis affects up to 37 million people worldwide and is most common in Africa. It is responsible for skin disease and blindness and is caused by a large worm (known as Onchocerca volvulus) which are passed as larvae 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 work their way through the skin tissue and mature into adult worms 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 (loss of colour in the skin). If the larvae travel to the eye, their death results in inflammation of the eye and 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, killing the bacteria with antibiotic drugs kills the worms and delivers a new and practical solution for treatment of onchocerciasis. The currently shortest-known treatment that is known 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 by using the combination of moxifloxacin and rifapentine.

Who can participate?
Healthy adults (18-55 years), microfilariae-positive (Mf+) with at least one medium-sized palpable nodule (onchocercoma).

What does the study involve?
Participants are randomly allocated to be given one of the following four treatment regimens:
1. Moxifloxacin plus rifapentine for 14 days
2. Moxifloxacin plus rifapentine for 7 days
3. Doxycycline 200 mg for 4 weeks
4. No treatment but nodulectomy (removing nodules) after 6 months

The treatment is given daily by a trial clinician. Six months after the start of the treatment all palpable nodules (onchocercomta) are removed under local anesthetic and sterile conditions by an experienced surgeon in a hospital. After discharge from the hospital, wound dressing are carried out by the research team until all wounds are healed. Before treatment, 3.5 months after treatment start and before removal of the nodules (6 months after treatment start), little skin biopsies (skin-snips) are taken to assess the number of larvae in the skin. Nodule sections are analysed under the microscope to find out whether the drug regimens work well 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 the start of the treatment. Following the nodulectomies, all participants are treated with a single dose of Ivermectin at the standard dose for mass drug administration (MDA) of 150µg/kg BW.

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 via the 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 communities of the Aowin / Suaman District in the Western Region of Ghana where onchocerciasis s endemic.

When is the study starting and how long is it expected to run for?
January 2014 to December 2019

Who is funding the study?
This study is partially funded by the BONFOR Research Commission of the Medical Faculty at Bonn and the Commission for Clinical Trials of the University Hospital Bonn.

Who is the main contact?
1. Dr. Alexander Yaw Debrah (public)
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2. Dr. Ute Klarmann-Schulz (scientific)
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Previous plain English summary:
Background and study aims
Onchocerciasis affects up to 37 million people worldwide and is most common in Africa. It is responsible for skin disease and blindness and is caused by a large worm (known as Onchocerca volvulus) which are passed as larvae 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 work their way through the skin tissue and mature into adult worms 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 (loss of colour in the skin). If the larvae travel to the eye, their death results in inflammation of the eye and 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, killing the bacteria with antibiotic drugs kills the worms and delivers a new and practical solution for treatment of onchocerciasis. The currently shortest-known treatment that is known 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 by using the combination of moxifloxacin and rifapentine.

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

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Participants are randomly allocated to be given one of the following four treatment regimens:
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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 via the 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 Ghana.

When is the study starting and how long is it expected to run for?
January 2014 to May 2017

Who is funding the study?
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Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
BONFOR 2014-11B-02

Study information

Scientific Title

Scientific title as of 05/12/2018:
The efficacy of Rifapentine 900mg/d plus Moxifloxacin 400mg/d given for 14 or 7 days against Onchocerciasis: a randomized, parallel-group, open-label, phase II pilot trial.

Previous scientific title:
The efficacy of Rifapentine 600mg/d plus Moxifloxacin 400mg/d given for 14 or 7 days against Onchocerciasis: a randomized, parallel-group, open-label, phase II pilot trial.

Acronym

MoRiOn

Study objectives

Study hypothesis as of 05/12/2018:
Wolbachia endosymbionts, present in most of the human filariae, are essential for worm fertility and survival. Treatment of onchocerciasis patients with doxycycline 200mg/d for 4 and 6 weeks resulted in Wolbachia depletion and female worm sterilization in both groups after 20 months. Studies carried out in in-vivo animal models showed that the combination of rifapentine plus moxifloxacin given for only 4-7 days also depleted Wolbachia numbers in adult worms to an extent even better (up to 3 logs) than what has been observed in the earlier human trials (2 logs).

Therefore the objectives of this trial are:
1. To show efficacy (Wolbachia depletion) of the combination Rifapentine plus Moxifloxacin in adult worms using immunohistology compared to no treatment and treatment with Doxycycline.
2. To show efficacy (Wolbachia depletion) of the combination Rifapentine plus Moxifloxacin in adult worms using PCR compared to no treatment and treatment with Doxycycline.
3. To analyze blockage of embryogenesis assessed by immunohistology us-ing the combination of Rifapentine plus Moxifloxacin compared to no treatment and treatment with Doxycycline.
4. To analyze the effect on microfilariae (Mf) in the skin using the combina-tion of Rifapentine plus Moxifloxacin
5. To analyze the effect on Wolbachia in the skin Mf by PCR using the com-bination of Rifapentine plus Moxifloxacin
6. To analyze the safety profile of the combination of Rifapentine plus Moxifloxacin in the treatment of Onchocerciasis
7. To select the best therapy strategy and dosing regimen with regard to safety and efficacy

Previous study hypothesis:
Wolbachia endosymbionts, present in most of the human filariae, are essential for worm fertility and survival. Treatment of onchocerciasis patients with doxycycline 200mg/d for 4 and 6 weeks resulted in Wolbachia depletion and female worm sterilization in both groups after 20 months [1]. Studies carried out in in-vivo animal models showed that the combination of rifapentine plus moxifloxacin given for only 4-7 days also depleted Wolbachia numbers in adult worms to an extent even better (up to 3 logs) than what has been observed in the earlier human trials (2 logs).
Therefore the objectives of this trial are:
1. To show efficacy (Wolbachia depletion) of rifapentine plus moxifloxacin
2. To provide a shortened treatment period using rifapentine plus moxifloxacin for 14 and 7 days
3. To show safety for treatment of onchocerciasis
4. To get parameter estimators for the sample size calculation of a subsequent confirmatory randomized controlled double blind phase II trial

Ethics approval required

Old ethics approval format

Ethics approval(s)
Ethics approval as of 05/12/2018:
1. The Committee for Human Research, Publication and Ethics (CHRPE) of the Kwame Nkrumah University of Science and Technology (KNUST), Kumasi, Ghana: approval: 22/11/2016; renewal: 04/05/2018
2. The Ghana Health Service Ethics Review Committee (GHS-ERC), Accra, Ghana: approval: 30/05/2017; renewal: 31/05/2018
3. The Ghana Food and Drug Authority (Ghana FDA), Accra, Ghana: approval: 13/10/2017; renewal: 15/10/2018
4. The Ethikkommission an der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms-Universität Bonn, Bonn, Germany: approval: 15/05/2017

Previous ethics approval:
Not provided at time of registration.

Study design
Single-centre, interventional, randomized, parallel-group, open-label, phase II pilot trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Home

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Onchocerciasis (River blindness)

Interventions
1. Experimental interventions:
Treatment regimen 1: Moxifloxacin 400mg/d plus rifapentine 900mg/d for 14 days (oral)
Treatment regimen 2: Moxifloxacin 400mg/d plus rifapentine 900mg/d for 7 days (oral)

2. Control interventions:
Treatment regimen 3: (Standard therapy): Doxycycline 200mg/d for 4 weeks (oral)
Treatment regimen 4: ("negative control"): No treatment but nodulectomy after 6 months

Additional treatment:
All participants (experimental and control interventions) will be treated with ivermectin (Mectizan®) at the standard MDA (mass drug administration) dosage of 150 µg/kg following the nodulectomies 6 months after study onset.

All treatment regimens will be administered by the trial clinician directly in the villages of the participants in form of daily observed treatment (DOT).

Follow-up per patient:
Onchocercomata will be removed under local anaesthesia in the hospital (nodulectomy) to assess Wolbachia, worm vitality and embryogenesis. The nodulectomies will be performed 6 months after the start of drug administration since Wolbachia depletion is completed after 4-5 months. Patients will be kept in hospital for the day of operation or one day longer (depending on the number of nodules ectomised) for observation before being discharged. Wound dressing will continue in the villages until all the wounds are healed (at least for 10 days after nodulectomy).

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
1. Moxifloxacin 2. Rifapentine 3. Doxycycline 4. Ivermectin

Primary outcome measure
Primary outcome measure as of 05/12/2018:
Absence of Wolbachia endobacteria in female adult worms assessed by immunohistology 6 months after treatment onset.

Previous primary outcome measure:
Absence of Wolbachia endobacteria in adult worms assessed by immuno-histology 6 months after treatment onset.

Secondary outcome measures
Secondary outcome measures as of 05/12/2018:
1. Reduction of Wolbachia bacteria in adult worms assessed by PCR 6 months after treatment onset.
2. Absence of Wolbachia bacteria in adult worms assessed by PCR 6 months after treatment onset.
3. Evaluation of worm embryogenesis assessed by histology in onchocercoma sections 6 months after treatment onset:
3.1. Normal embryos
3.2. Degenerated embryos
3.3. No embryos/uterus empty
4. Reduction of microfilariae in the skin 3.5 and 6 months after treatment onset.
5. Absence of microfilariae in the skin 3.5 and 6 months after treatment onset.
6. Reduction of the Wolbachia in the skin Mf 3.5 and 6 months after treatment onset assessed by

PCR.
7. Adverse events (AEs) as well as serious adverse events (SAEs) in response to the different treatments will be assessed and described in the scope of the daily observed treatment (DOT).

Previous secondary outcome measures:
1. Reduction of Wolbachia bacteria in adult worms assessed by PCR 6 months after treatment onset
2. Absence of Wolbachia bacteria in adult worms assessed by PCR 6 months after treatment onset
3. Reduction of microfilariae in the skin 6 months after treatment onset
4. Absence of microfilariae in the skin 6 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. Assessment of safety: Adverse events (AEs) will be assessed and described in the scope of the daily observed treatment (DOT):
6.1. Occurrence of an AE
6.2. Intensity of AE (Grade 0 (None); Grade 1 (Mild): No effect on activities of daily life; Grade 2 (Moderate): Daily life activities are partially limited (can complete ≥ 50% of necessary activities); Grade 3 (Severe): Daily life activities are severely restricted (can complete < 50% of necessary activities))
6.3. SAE?
6.4. Relation to treatment (definite, probable, possible, remote, not related)
6.5. Intervention
6.6. Outcome of AE (resolved spontaneously, resolved with treatment, resolved with residual effect, unchanged/ not resolved, death)

Overall study start date
26/01/2014

Completion date
31/12/2019

Eligibility

Key inclusion criteria
Participant inclusion criteria as of 05/12/2018:
1. Willingness to participate in the study by signing the Informed Consent Form (ICF)
2. 18-55 years
3. Body weight > 45kg
4. Presence of at least 1 medium-sized onchocercoma detected by palpation
5. Mf-positive
6. Good general health without any clinical condition requiring medication
7. No previous history of tuberculosis
8. Participants with the ability to follow study instructions and are likely to attend and complete all required visits

Previous participant inclusion criteria:
1. Men and Women
2. 18-55 years

3. Body weight > 45kg
4. Presence of at least 3 onchocercomata detected by palpation
5. Mf-positive
6. Good general health without any clinical condition requiring long-term medication
7. No previous history of tuberculosis
8. Participants with the ability to follow study instructions and are likely to attend and complete all required visits
9. Willingness to participate in the study by signing the Informed 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
80

Key exclusion criteria
Participant exclusion criteria as of 05/12/2018:
General Exclusion Criteria:
1. Participants not able to give consent
2. Participants who are unable to understand the nature, scope, significance and consequences of this clinical trial
3. Participants taking any concomitant medication
4. Known history of hypersensitivity to the investigational drug or to drugs with a similar chemical struc-ture (moxifloxacin or any member from the quinolone class, rifapentine or any member of the rifamycins, doxycycline or any member of the tetracyclines)
5. Simultaneous participation in any clinical trial involving administration of an investigational medicinal product within 30 days prior to clinical trial beginning
6. Participants with a physical or psychiatric condition which at the investigator’s discretion may put the subject at risk, may confound the trial results, or may interfere with the subject’s participation in this clinical trial
7. Known or persistent abuse of medication, drugs or alcohol

Exclusion criteria regarding special restrictions for females:
1. Pregnant women
2. Breastfeeding women
3. Females of childbearing potential, who are not willing or able to use methods to prevent a pregnancy for the entire treatment duration in addition to hormonal contraception (e.g. condoms) unless they are surgically sterilized / hysterectomized or there are any other criteria considered sufficiently reliable by the investigator in individual cases.

Indication specific exclusion criteria:
1. History or clinical signs of tuberculosis or treatment against TB
2. History of porphyria
3. History or clinical signs of arrhythmia
4. Bradycardia (< 50bpm)
5. QT-prolongation (QT interval >440 msec for men and >460 msec for women)
6. History of tendinitis or tendon rupture
7. History of rheumatoid arthritis
8. History of myasthenia gravis or polio
9. History of cerebral disorder (e.g. epilepsy)
10. History of photosensitivity/phototoxicity
11. History of Diabetes mellitus (in addition urine examination for glucose)
12. 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
13. Evidence of acute Hepatitis A and of acute or chronic Hepatitis B or C
14. Laboratory evidence of liver disease (AST, ALT, gammaGT, Bilirubin greater than the upper limit of normal)
15. Laboratory evidence of renal disease (serum creatinine greater than 1.5 times upper limit of normal)
16. Laboratory evidence of low or high potassium level (potassium level < 3.6 or > 5.2)
17. Laboratory evidence of leucopenia (< lower limit of normal)

Previous participant exclusion criteria:
1. Pregnant women
2. Breastfeeding women
3. Participants not able to give consent
4. Participants without legal capacity who are unable to understand the nature, scope, significance and consequences of this clinical trial
5. Known history of hypersensitivity to the investigational drug or to drugs with a similar chemical structure (moxifloxacin or any member from the quinolone class, rifapentine or any member of the rifamycins, doxycycline or any member of the tetracyclines)
6. Simultaneously participation in another clinical trial or participation in any clinical trial involving administration of an investigational medicinal product within 30 days prior to clinical trial beginning
7. Participants with a physical or psychiatric condition which at the investigator’s discretion may put the subject at risk, may confound the trial results, or may interfere with the subject’s participation in this clinical trial
8. Known or persistent abuse of medication, drugs or alcohol
9. Indication specific exclusion criteria
10. History or clinical signs of tuberculosis or treatment against TB
11. History of porphyria
12. History or clinical signs of arrhythmia
13. History of tendinitis or tendon rupture
14. History of myasthenia gravis
15. History of photosensitivity/phototoxicity
16. Diabetes (assessed by history of participants and urine examination)
17. 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
18. Laboratory evidence of liver disease (AST, ALT, µGT, Bilirubin greater than the upper limit of

normal)
19. Laboratory evidence of renal disease (serum creatinine greater than 1.5 times upper limit of normal)
20. Laboratory evidence of low or high potassium level (potassium level < 3.6 or > 5.2)

Date of first enrolment
01/10/2018

Date of final enrolment
31/01/2019

Locations

Countries of recruitment
Ghana

Study participating centre
Kumasi Centre for Collaborative Research (KCCR)
Kwame Nkrumah University of Science and Technology (KNUST)
Kumasi
Ghana
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Sponsor information

Organisation
Kumasi Centre for Collaborative Research (KCCR)

Sponsor details
Kwame Nkrumah University of Science and Technology (KNUST)
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0000

Sponsor type
Research organisation

Website
http://kccr-ghana.org/

ROR
https://ror.org/032d9sg77

Funder(s)

Funder type
Not defined

Funder Name
BONFOR Research Commission of the Medical Faculty at Bonn University (Germany)

Funder Name
Commission for Clinical Trials of the University Hospital Bonn (Germany)

Results and Publications

Publication and dissemination plan

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration