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Exploratory efficacy assessment of Rifampicin and Albendazole to treat Onchocerciasis in areas of co-endemicity with Loiasis

Submission date
22/02/2021

Recruitment status
No longer recruiting

Registration date
04/06/2021

Overall study status
Ongoing

Last Edited
13/05/2024

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

Background and study aims

River blindness (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 microfilariae travel to the eye, it can result in inflammation of the eye and ultimately to blindness.

The current therapeutic strategy relies on annual mass drug administration (MDA) with the drug Ivermectin (IVM). IVM kills the microfilariae but after a few months following treatment female adult worms start to produce new microfilariae high enough for transmission. Additionally, there is another filarial worm called Loa loa in the rain forest of Central Africa, which can cause the disease loiasis. People who have microfilariae from Loa loa can develop severe adverse reactions when taking IVM. Therefore, it is very difficult to do MDA in areas where people may be co-infected with onchocerciasis and loiasis and this has contributed to failure of IVM-MDA programmes.

Onchocerca volvulus has a unique feature shared with some other closely related worm species: it lives in 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 specific antibiotic drugs can lead to death or long-term sterility of the adult female worms and delivers a new and practical solution for the treatment of onchocerciasis. On the contrary, Loa loa does not contain Wolbachia.

The currently shortest-known treatment that is known to lead to death or long-term sterility of Onchocerca volvulus is doxycycline 200 mg/ day given for 4 weeks. The aim of this study is to shorten the treatment period further by using combinations of albendazole with either rifampicin or doxycycline and to show that these treatment regimen are also safe for patients co-infected with Loa loa.

Who can participate:
Participants aged 18 - 55 years with the presence of at least 1 onchocerca nodule detected by palpation and Onchocerca volvulus microfilaria positive will be recruited into the study.

What does the study involve:
In participants with onchocerciasis mono-infection, the combination of rifampicin (35 or 10 mg /kg) plus albendazole (400 mg) given for 7 or 14 days will be tested and compared to a group receiving standard therapy (IVM at 3.5 months and after nodulectomies at 18 months). A combination of doxycycline (200 mg) plus albendazole (400 mg) will also be tested for 14 days. The standard dose of 200 mg doxycycline for 28 days will be used as a control group as well as albendazole alone 400mg/d for 14 days. Additionally, the combination of rifampicin (35 or 10mg /kg) plus albendazole (400mg) and doxycycline 200mg for 28 days will be tested in participants with onchocerciasis/loiasis co-infection.

What are the possible benefits and risks of participating:
All participants will benefit from this trial even if they do not belong to the experimental intervention groups or the doxycycline group. They will all have their onchocercomata removed 18 (+3) months after treatment onset and the mono-infected people will be treated at 3.5 (+1) months and immediately after nodulectomy with Ivermectin at the standard MDA dosage of 150 µg/kg.
The potential risks for the participants arise from the study drugs, the blood drawing, the skin snips and the surgeries (nodulectomies).

Where is the study run from:
This is a mono-center trial carried out by the Parasite and Vector Biology Research Unit, University of Buea. The study participants will be recruited from the communities of the Loum, Manjo, Melong, Kumba, Nkongsamba, Yabassi, Nkonjock, Edea, Ngambe, Pouma and Bafia Health Districts, situated in the Nkam-Wouri, Sanaga, Mbam, and Meme river basins in Cameroon. The trial will be set up in the Manjo Hospital.

When is the study starting and how long is it expected to run for:
January 2021 to December 2025

Who is funding the study:
The funding for this trial was received by the European and Developing Countries Clinical Trial Partnership (EDCTP) and the German Center for Infection Research (DZIF) which is funded by the German Federal Ministry of Education and Research.

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
EDCTP-ESRIFAL-01

Study information

Scientific Title
Exploiting the synergy of registered drugs Rifampicin and Albendazole to shorten the treatment duration of Macrofilaricide for the cure of Onchocerciasis in areas co-endemic with Loiasis: An exploratory Pilot phase II Clinical Trial study

Acronym
ESRiFAL

Study objectives
Current study hypothesis as of 09/02/2024:

Administration of high-dose RIF plus ALB for 7 or 14 days will have a macrofilaricidal effect or lead to permanent sterility of the living female adult O. volvulus worms without inducing adverse and severe adverse reactions in individuals co-infected with Loa loa.

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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 200 mg/day 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 elevated exposures of orally-administered rifampicin can lead to Wolbachia depletions from filariae more rapidly than those achieved by doxycycline. Dose escalation of rifampicin achieves >90% Wolbachia depletion in time periods of 7 days in B. malayi and 14 days in O. ochengi. In a second study the combination of rifampicin plus albendazole given for only 7 days also depleted Wolbachia numbers in adult worms, blocked embryogenesis, and stopped microfilariae production. These pre-clinical observations need confirmation in a trial study.

Ethics approval required
Ethics approval required

Ethics approval(s)

1. Approved 11/10/2023, Comite National D'Ethique de la Recherche pour la Sante Humaine (CNERSH) (Ministry of Public Health, Yaounde, -, Cameroon; -; Cnethique_minsante@yahoo.fr), ref: N°2023/10/1586/CE/CNERSH/SP

2. Approved 26/01/2024, Ethikkommission der Medizinischen Fakultät der Rheinischen Friedrich-Wilhelms Universität Bonn (Venusberg-Campus 1, Bonn, 53127, Germany; +4922828751931; ethik@ukbonn.de), ref: 362/23-EP

Previous ethics details:

1. Approved 15/06/2020, Cameroon National Ethics Committee for Human Health Research (CNERSH) (Cameroon National Ethics Committee, P. O. Box 1937, Yaoundé, Cameroon; +237 000 2221 1284; no email provided), ref: 976
2. Approval pending, Ethikkommission an der Medizinischen Fakultaet der Rheinischen Friedrich-Wilhelm-Universitaet Bonn (Bonn, Germany)

Study design
Prospective randomized controlled monocentric open-label parallel-group interventional phase II pilot trial with blinded endpoint evaluation

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Community, Home, Hospital

Study type(s)
Treatment, Safety, Efficacy

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

Health condition(s) or problem(s) studied
Onchocerciasis (river blindness), Loiasis

Interventions
Current interventions as of 09/02/2024:

The study is a prospective, randomized, controlled, monocentric, open-label, parallel-group, interventional phase II pilot trial with blinded endpoint evaluation as the histologists and the persons responsible for PCR assessment will be blinded to treatment assignment. Patients with onchocerciasis mono-infection (group "a") or onchocerciasis/loiasis co-infection (group "b") who meet the inclusion criteria will be allocated to participate in this clinical trial and finally randomized to one of the seven following treatment groups (“a” is always for onchocerciasis mono-infection, “b” is always for onchocerciasis/loiasis co-infection):

1. Experimental Interventions:
Treatment 1a and 1b: rifampicin 35 mg/kg + albendazole 400 mg/d for 14 days (oral)
Treatment 2a: rifampicin 35 mg/kg + albendazole 400 mg/d for 7 days (oral)
Treatment 3a and 3b: rifampicin 10 mg/kg + albendazole 400 mg/d for 14 days (oral)
Treatment 4a: doxycycline 200 mg + albendazole 400 mg/d for 14 days (oral)

2. Control Interventions:
Treatment 5a and 5b: doxycycline 200 mg for 4 weeks
Treatment 6a: albendazole 400mg for 14 days
Treatment 7a: Standard of care (IVM at 3.5 (+1) and 18 (+3) months)

Additional treatment:
All participants (in experimental and control interventions) with onchocerciasis mono-infection will be treated (if present) with a single dose of Ivermectin (Mectizan®/Merck) at the standard MDA dosage according to standard care and participant's weight at 3.5 (+1) and 18 (+3) months after treatment onset (after samples have been taken for the follow up analyses).

Follow-up per patient:
The onchocercomata of all participants will be removed under local anesthesia in the Manjo Hospital (nodulectomy) by the trial surgeon at 18 (+3) months after treatment onset to assess the effect of the drugs on embryogenesis, Wolbachia and vitality of the adult female worms. Participants 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.

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Previous interventions:

The study is a prospective, randomized, controlled, monocentric, open-label, parallel-group, interventional phase II pilot trial with blinded endpoint evaluation as the histologists and the persons responsible for PCR assessment will be blinded to treatment assignment. Patients with onchocerciasis who meet the inclusion criteria will be allocated to participate in this clinical trial and finally randomized to one of the six following treatment groups:

1. Experimental Interventions:
Treatment A: rifampicin 35 mg/kg + albendazole 400 mg/d for 14 days (oral)
Treatment B: rifampicin 35 mg/kg + albendazole 400 mg/d for 7 days (oral)
Treatment C: rifampicin 10 mg/kg + albendazole 400 mg/d for 14 days (oral)
Treatment D: doxycycline 200 mg + albendazole 400 mg/d for 14 days (oral)

2. Control Interventions:
Treatment E (standard therapy): doxycycline 200 mg for 4 weeks
Treatment F (control): Albendazole 400mg for 14 days
Treatment G (control): Albendazole 400mg for 7 days
Treatment H (control): nodulectomy only

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 (after exclusion of participants infected with Loa loa).
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)
albendazole, rifampicin, doxycycline, ivermectin

Primary outcome measure
Current primary outcome measure as of 09/02/2024:

Evaluation of adult female worm embryogenesis assessed by immunohistology 18 (+3) months after treatment onset:

a. normal embryos
b. degenerated embryos
c. no embryos.

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Previous primary outcome measure:

Absence of Wolbachia endobacteria in adult female worms assessed by immunohistology 6 months after treatment onset

Secondary outcome measures
Current secondary outcome measures as of 09/02/2024:

1. Absence of Wolbachia endobacteria in adult female worms assessed by immunohistology 18 (+3) months after treatment onset.
2. Reduction of Wolbachia bacteria in the nodules assessed by PCR 18 (+3) months after treatment onset.
3. Proportion of dead and alive female adult worms assessed by immunohistology at 18 (+3) months after treatment onset.
4. Reduction of OV MF in the skin at 3.5, 6, 12 and 18 (+3) months after treatment onset.
5. Absence of OV MF in the skin at 3.5, 6, 12 and 18 (+3) months after treatment onset.
6. Reduction of the Wolbachia in the skin OV MF assessed by PCR at 3.5, 6, 12 and 18 (+3) months after treatment onset.
7. Reduction of LL MF in the blood at 3.5, 6, 12 and 18 (+3) months after treatment onset (only treatment groups 1b, 3b and 5b).
8. Absence of LL MF in the blood at 3.5, 6, 12 and 18 (+3) months after treatment onset (only treatment groups 1b, 3b and 5b).

9. Lack of Serious Adverse Events (SAEs) related to the activity of the combination of RIF plus ALB or DOX alone in participants co-infected with Onchocerca volvulus and Loa loa.
10. 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).

11. Preparation of a pharmacokinetic profile for the combinations RIF + ALB and DOX + ALB compared to the profile of DOX or ALB alone (PK-subgroup)

Previous secondary outcome measures:

1. Wolbachia bacteria in adult worms assessed by PCR at baseline and 6 months after treatment onset
2. Evaluation of worm embryogenesis assessed by histology 6 months after treatment onset:
2.1. Normal embryos
2.2. Degenerated embryos
2.3. No embryos
3. Microfilariae in the skin at baseline, 3.5 and 6 months after treatment onset
4. Wolbachia in the skin MF assessed by PCR at baseline, 3.5 and 6 months after treatment onset
5. Adverse events (AEs) as well as Serious Adverse Events (SAEs) in response to the different treatments assessed and described in the scope of the daily observed treatment (DOT)

Overall study start date
01/01/2021

Completion date
31/12/2025

Eligibility

Key inclusion criteria
Current inclusion criteria as of 09/02/2024:

1. Willingness to participate in the study by signing the Informed Con- sent Form (ICF)
2. Age: 18-55 years
3. Body weight: 50 – 90 kg
4. Presence of at least one Onchocerca nodule detected by palpation
5. OV MF-positive
6. LL MF negative (group “a”)
7. LL MF positive: < 8.000 MF (group “b” only)
8. Good general health without any clinical condition requiring medication
9. No previous history of tuberculosis
10. Negative for active TB (PCR analysis)
11. Participants with the ability to follow study instructions and are likely to attend and complete all required visits

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Previous inclusion criteria:

1. Willingness to participate in the study by signing the Informed Consent Form (ICF)
2. 15 - 55 years
3. Bodyweight ≥50 kg
4. Presence of at least 2 medium-sized or one large Onchocerca nodule 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

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Upper age limit
55 Years

Sex
Both

Target number of participants
240

Key exclusion criteria
Current exclusion criteria as of 09/02/2024:

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 (i.e. medication that cannot be discontinued during the trial; Women taking hormonal contraceptives should continue to take it, but they have to agree to use additional methods of contraception). Supplements (e.g.vitamins (with the exception of vitamin D which is contraindicated)) are allowed.
4. Known history of hypersensitivity to the investigational drug or to drugs with a similar chemical structure (RIF or any member of the Rifamycins (e.g. Rifapentin, Rifaximin), ALB or any member of the Benzimidazole group (e.g. Mebendazole), DOX or any member of the Tetracyclines (e.g. Chlortetracyclin, Minocyclin))
5. Treatment with the trial drugs rifampicin or doxycycline during the previous year.
6. Simultaneous participation in any clinical trial.
7. Participants with a physical or psychiatric condition which at the
8. investigator’s discretion may put the participant at risk, may confound the trial results, or may interfere with the participation in this clinical trial
9. Known or persistent abuse of medication, drugs or alcohol
10. Pregnant women
11. Breastfeeding women

12. Women of childbearing potential, who are not willing or able to use methods to prevent a pregnancy for the entire treatment duration plus additional 4 weeks after treatment end 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
13. Men with partners of childbearing potential, who are not willing or able to use methods to prevent a pregnancy (e.g. condoms) for the entire treatment duration plus additional 4 weeks after treatment end

Indication specific exclusion criteria:
1. History or clinical signs of Tuberculosis (TB) or treatment against TB
2. Positive for active TB (PCR analysis)
3. History of Porphyria
4. History of photosensitivity/phototoxicity
5. History of Diabetes mellitus (in addition to dipstick test for glycosuria)
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
7. Evidence of acute Hepatitis A and of acute or chronic Hepatitis B or C
8. Laboratory evidence of liver disease (AST, ALT, γGT greater than the upper limit of normal, total bilirubin greater than 1.5 the upper limit of normal)
9. Laboratory evidence of renal disease (serum creatinine greater than the upper limit of normal)
10. Laboratory evidence of Leukopenia (leukocytes < 4.00 $*10^3/\mu L$)
11. Laboratory evidence of thrombocytopenia (platelets count <150,000/mm^3)
12. Laboratory evidence of anemia (Hemoglobin levels <8g/dL)
13. Laboratory evidence of Glycosuria (dipstick ≥ 1+) or proteinuria (dip- stick ≥ 2+)
14. LL MF positive (group “a”)
15. LL MF > 8,000 MF (group “b”)

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Previous exclusion criteria:

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 co-infected with Loa Loa
4. Participants taking any concomitant medication (i.e. medication that cannot be discontinued during the trial; women taking hormonal contraceptives should continue to take it, but they have to agree to use additional methods of contraception)
5. Known history of hypersensitivity to the investigational drug or to drugs with a similar chemical structure (rifampicin or any member of the rifamycins, albendazole or any member of the benzimidazole group, doxycycline or any member of the tetracyclines)
6. Simultaneous 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

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 of photosensitivity/phototoxicity
4. History of Diabetes mellitus (in addition to dipstick test for glycosuria)
5. 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
6. Evidence of acute Hepatitis A and of acute or chronic Hepatitis B or C
7. Laboratory evidence of liver disease (AST, ALT, γGT greater than the upper limit of normal, total bilirubin greater than 1.5 the upper limit of normal)
8. Laboratory evidence of renal disease (serum creatinine greater than the upper limit of normal)
9. Laboratory evidence of leukopenia (leukocytes < 4,000 WBC/ml), thrombocytopenia (platelets count <150000/µL) and Hemoglobin levels (<8g/dl).
10. Laboratory evidence of glycosuria (dipstick ≥ +) or proteinuria (dipstick ≥2+)

Date of first enrolment
12/02/2024

Date of final enrolment
30/09/2024

Locations

Countries of recruitment
Cameroon

Study participating centre
University of Buea
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Funder type
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Funder Name
European and Developing Countries Clinical Trial Partnership (EDCTP) and German Center for Infection Research (DZIF)

Results and Publications

Publication and dissemination plan
It is planned to publish the results in a peer-reviewed scientific journal.

Intention to publish date
30/06/2026

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date