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Doxycycline to improve filarial lymphedema (LEDoxy Tanzania)

Submission date
21/07/2017

Recruitment status
Recruiting

Registration date
25/07/2017

Overall study status
Ongoing

Last Edited
18/12/2024

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
Lymphatic filariasis is a parasitic disease caused by microscopic, thread-like worms that infect the lymph system, resulting in fluid collection and swelling (lymphedema). Current lymphedema treatment is based on the use of simple measures of hygiene (regular washing with soap and water, skin and nail care), use of topical antibiotics or antifungal agents, exercise and footwear. This is considered the "standard of care" and has been shown to reduce the frequency of acute attacks that drive the progression of lymphedema. In two previous studies, doxycycline 200mg was given to patients with lymphedema for six weeks. This oral antibiotic treatment led to improvement or halt of the progression of the lymphedema in most of the treated patients despite active infection with worms that cause lymphatic filariasis. In order to expand the benefits of this observation to more people affected by this disease, similar studies are needed to confirm the earlier results so that doxycycline treatment can be introduced into current treatment programmes. This study takes place in Tanzania and is one of five studies that have the aim to confirm the effect of doxycycline 200mg for 6 weeks. The other four studies are carried out in Mali, Sri Lanka, India and Ghana. While the three studies in Mali, Sri Lanka and India compare doxycycline 200 mg for six weeks versus a placebo (dummy drug) matching doxycycline (both treatments on top of standard methods of hygiene), the two studies in Tanzania and Ghana have the additional aim to find out whether a lower dose of doxycycline of 100mg is equally beneficial.

Who can participate?
Patients aged 14 – 65 with a lymphedema of the leg

What does the study involve?
Participants with lymphedema stage 1-3 are randomly allocated to be treated with either doxycycline 200mg, doxycycline 100mg or a placebo for six weeks, and participants with lymphedema stage 4-6 are randomly allocated to receive doxycycline 200mg or a placebo for six weeks. All treatments are given in addition to the standard methods of hygiene and mass drug administration (ivermectin 200µg/kg plus albendazole 400mg) in areas where this is still ongoing. At the start of the study and 6, 12, 18 and 24 months later, participants undergo measurements of the leg. A questionnaire about the occurrence of acute attacks is carried out every two months after treatment onset. Participants also undergo lymphedema management

training at the start of the study and after four, six, 12, 18 and 24 months. All people seen by the team at the study start (those who received treatment and those who had to be excluded) will be asked to consent to an additional follow-up around three years after treatment start which will consist of similar procedures as the follow-up after 24 months. In addition, we will ask some questions related to COVID-19. All participants will receive another round of lymphedema management training including the necessary supplies.

What are the possible benefits and risks of participating?
Benefits to the participant include thorough medical evaluation, intensified hygiene training, free supplies for local care of lymphedema and free medical treatment for common illnesses during the treatment period and follow-up. The risks to participants are side effects caused by the licensed study drug doxycycline and infection during blood sampling. In the event of side effects caused by the study drugs or treatments, participants are treated and followed up by the research team until they are resolved.

Where is the study run from?
The National Institute of Medical Research (NIMR) (Tanzania)

When is the study starting and how long is it expected to run for?
January 2017 to December 2025

Who is funding the study?
Research Networks for Health Innovations in Sub-Saharan Africa sponsored by the Federal Ministry of Education and Research (BMBF) (Germany)

Who is the main contact?
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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
TAKeOFF-4-0117-TZ

Study information

Scientific Title
Doxycycline 200mg/d vs 100mg/d for 6 weeks to improve filarial lymphedema: a multi-national, double-blind, randomized, placebo-controlled trial

Acronym
TAKeOFF - LEDoxy

Study objectives
Hypotheses for Group A (LE stage 1-3):
1. To confirm the efficacy of a 6-week course of daily doxycycline 200mg on lack of progression of filarial lymphedema (LE).
2. To reduce the dosage of doxycycline from 200mg/d to 100mg/d for 6 weeks for the treatment of filarial LE.

Hypothesis for Group B (LE stage 4-6):
1. To show efficacy of a 6-week course of daily doxycycline 200mg on lack of progression of filarial LE.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Medical Research Coordinating Committee (MRCC, NIMR)/ Ministry of Health, Community Development, Gender, Elderly & Children, Dar es salaam, Tanzania: approval for first submission: 19/02/2018; approval for first amendment: 22/06/2018
2. Tanzania Food and Drug Authority, Dar es salaam,Tanzania: approval for first submission (incl.

first amendment): 28/06/2018
3. Ethikkommission an der Medizinischen Fakultaet der Rheinischen Friedrich-Wilhelms-Universitaet Bonn, Bonn, Germany: approval for first submission: 06/12/2017; approval for first amendment: 12/07/2018
4. Ethikkommission bei der Med. Fakultät der LMU München: : approval for first submission: 25 /01/2018; approval for first amendment: 01/07/2018

Study design
Multi-national interventional randomized double-blind placebo-controlled phase II 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
Lymphatic filariasis (LF)

Interventions
Current interventions as of 03/08/2018 to 18/12/2024:
The study involves daily observed treatment with either doxycycline 200mg for 6 weeks, doxycycline 100mg for 6 weeks or placebo matching doxycycline for 6 weeks (42 days). Participants with lymphedema stage 1-3 are randomised using block randomisation to one of the three treatment regimens, participants with lymphedema stage 4-6 receive either doxycycline 200mg or placebo matching doxycycline.

1. DOX 200: Doxycycline 200mg/d for six weeks (2 100mg tablets/day orally) on top of standard MDA (ivermectin 200µg/kg plus albendazole 400mg once a year)

2. Placebo (control): Placebo matching Doxycycline for six weeks (2 tablets/day orally) on top of standard MDA (ivermectin 200µg/kg plus albendazole 400mg once a year)

3. DOX 100 (additional arm for group A [LE stage 1-3]): Doxycycline 100mg/d for six weeks (1 tablet 100mg doxycycline/day plus one tablet placebo matching doxycycline orally) on top of standard MDA (ivermectin 200µg/kg plus albendazole 400mg once a year)

Treatment is administered ad personam by the trial clinician directly in the villages in the form of daily observed treatment (DOT). All treatment regimens is administered on top of the standardized methods of hygiene ("standard of care") and on top of standard mass drug administration (MDA; ivermectin 200µg/kg plus albendazole 400mg) in areas where MDA is still

ongoing. Treatment is carried out in a blinded manner, meaning that neither the patients nor the caregiver know to which treatment arm the patients belong.

At baseline as well as six, 12, 18 and 24 months after treatment onset as well as minimum 2 years after the last contact with the participants, participants undergo lymphedema-specific measurements (circumference measurements of the leg, volume measurement of the legs). A questionnaire regarding the occurrence of acute attacks (ADLA) is carried out every two months after treatment onset. Participants also undergo lymphedema management training at baseline and after four, six, 12, 18 and 24 months.

Minimum two years after the last contact with the study team, participants who consent in a separate form will again undergo lymphedema-specific measurements (staging, circumference measurements of the leg, volume measurement of the legs). A questionnaire regarding the occurrence of acute attacks (ADLA) and about hygiene and lymphedema management will be carried out. Participants will also undergo another lymphedema management training.

Previous interventions as of 03/08/2018 to 18/12/2024:
The study involves daily observed treatment with either doxycycline 200mg for 6 weeks, doxycycline 100mg for 6 weeks or placebo matching doxycycline for 6 weeks (42 days). Participants with lymphedema stage 1-3 are randomised using block randomisation to one of the three treatment regimens, participants with lymphedema stage 4-6 receive either doxycycline 200mg or placebo matching doxycycline.

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Treatment is administered ad personam by the trial clinician directly in the villages in the form of daily observed treatment (DOT). All treatment regimens is administered on top of the standardized methods of hygiene ("standard of care") and on top of standard mass drug administration (MDA; ivermectin 200µg/kg plus albendazole 400mg) in areas where MDA is still ongoing. Treatment is carried out in a blinded manner, meaning that neither the patients nor the caregiver know to which treatment arm the patients belong.

Previous interventions:
At baseline as well as six, 12, 18 and 24 months after treatment onset, participants undergo lymphedema-specific measurements (circumference measurements of the leg, volume measurement of the legs). A questionnaire regarding the occurrence of acute attacks (ADLA) is carried out every two months after treatment onset. Participants also undergo lymphedema management training at baseline and after four, six, 12, 18 and 24 months.

Previous interventions:
At baseline as well as six, 12 and 24 months after treatment onset, participants undergo lymphedema-specific measurements (circumference measurements of the leg, volume measurement of the legs, ultrasound measurement of the skin thickness at the ankles). A questionnaire regarding the occurrence of acute attacks (ADLA) is carried out every two months

after treatment onset. Participants also undergo lymphedema management training at baseline and after four, six, 12, 18 and 24 months.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome measure
Lack of progression of lymphedema (LE) (stage reduction or same stage as pre-treatment using the 7-point scale staging according to Dreyer et al, 2002), examined 24 months after treatment onset

Secondary outcome measures
Current secondary outcome measures as of 18/12/2024:
1. Lack of progression of LE (stage reduction or same stage as pre-treatment using the 7-point scale staging according to Dreyer et al., 2002), examined 6, 12 or 18 months after treatment onset and at the Follow-Up Visit
2. Improvement of LE, i.e. stage reduction (at least one stage compared to pre-treatment), examined 6, 12, 18 and 24 months after treatment onset and at the Follow-Up Visit
3. Change of LE stages (reduction or increase) compared to baseline, assessed at 6, 12, 18 and 24 months after treatment onset and at the Follow-Up Visit
4. Changes (reduction or increase) of the circumference of the affected limbs compared to baseline circumferences, measured by tape measure at 6, 12 and 24 months after treatment onset and at the Follow-Up Visit
5. Changes in skin thickness of the affected limbs compared to baseline values, measured by ultrasound at 6, 12 and 24 months after treatment onset (outcome measure removed as of 03/08/2018)
6. Changes in the circumference of the affected limbs compared to baseline circumferences, measured with an infrared scanner (LymphaTech®) at 6, 12 and 24 months after treatment onset and at the Follow-Up Visit
7. Changes in the volume of the affected limbs compared to baseline volume, measured with an infrared scanner (LymphaTech®) at 6, 12 and 24 months after treatment onset and at the Follow-Up Visit
8. Changes in the duration of acute attacks compared to pre-treatment, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset and at the Follow-Up Visit
9. Changes in the frequency of acute attacks compared to pre-treatment, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset and at the Follow-Up Visit
10. Absence of acute attacks, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset and at the Follow-Up Visit
11. Changes in the hygiene level compared to pre-treatment, assessed by using a hygiene survey especially developed for this study at 6, 12 and 24 months and at the Follow-Up Visit
12. Changes in the quality of life (QoL) compared to pre-treatment, assessed using the 12-item version of the WHODAS 2.0 at 12 and 24 months after treatment onset and at the Follow-Up

Visit
13. Levels of angiogenic, lymphangiogenic, pro-fibrotic or pro-inflammatory biomarkers (such as VEGF, CECAM-a, MMPS) in blood and/or urine as a measure for prognostic effects, measured using ELISA and/or Luminex Multiplex Assay technique at baseline, 6, 12 and 24 months after treatment onset
14. T cell activation and differentiation markers in the blood such as HLADR, Ki67 and CD38 (activation), PD-1, CTLA-4, Eomes (exhaustion), CD45RA, CD27, CCR7 (differentiation) on CD4 and CD8 T cells, assessed using unstimulated whole blood which will be added to fluorochrome-conjugated antibodies that specifically detect the above-mentioned factors. The percentage of positive cells is measured using flow cytometry at baseline, 6, 12 and 24 months after treatment onset

Assessment of safety:
Adverse events (AE) assessed and described in the scope of the daily observed treatment (DOT). This involves: a) occurrence of AE, b) intensity of AE (Grade 0 [none], Grade 1 [mild], grade 2 [moderate] grade 3 [severe], c) SAE, d) relation to treatment (definite, probable, possible, remote, not related), e) outcome of AE (restored, improved, unchanged, deteriorated, death, unknown, overcome with sequelae, f) intervention

Previous secondary outcome measures:
1. Lack of progression of LE (stage reduction or same stage as pre-treatment using the 7-point scale staging according to Dreyer et al., 2002), examined 6, 12 or 18 months after treatment onset
2. Improvement of LE, i.e. stage reduction (at least one stage compared to pre-treatment), examined 6, 12, 18 and 24 months after treatment onset
3. Change of LE stages (reduction or increase) compared to baseline, assessed at 6, 12, 18 and 24 months after treatment onset
4. Changes (reduction or increase) of the circumference of the affected limbs compared to baseline circumferences, measured by tape measure at 6, 12 and 24 months after treatment onset
5. Changes of skin thickness of the affected limbs compared to baseline values, measured by ultrasound at 6, 12 and 24 months after treatment onset (outcome measure removed as of 03/08 /2018)
6. Changes of the circumference of the affected limbs compared to baseline circumferences, measured with an infrared scanner (LymphaTech®) at 6, 12 and 24 months after treatment onset
7. Changes of the volume of the affected limbs compared to baseline volume, measured with an infrared scanner (LymphaTech®) at 6, 12 and 24 months after treatment onset
8. Changes in the duration of acute attacks compared to pre- treatment, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset
9. Changes in the frequency of acute attacks compared to pre-treatment, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset
10. Absence of acute attacks, as assessed with a questionnaire every two months after treatment onset and evaluated at 6, 12 and 24 months after treatment onset
11. Changes of the hygiene level compared to pre-treatment, assessed by using a hygiene survey especially developed for this study at 6, 12 and 24 months
12. Changes of the quality of life (QoL) compared to pre-treatment, assessed using the 12-item version of the WHODAS 2.0 at 12 and 24 months after treatment onset
13. Levels of angiogenic, lymphangiogenic, pro-fibrotic or pro-inflammatory biomarkers (such as VEGF, CECAM-a, MMPS) in blood and/or urine as a measure for prognostic effects, measured using ELISA and/or Luminex Multiplex Assay technique at baseline, 6, 12 and 24 months after

treatment onset
14. T cell activation and differentiation markers in the blood such as HLADR, Ki67 and CD38 (activation), PD-1, CTLA-4, Eomes (exhaustion), CD45RA, CD27, CCR7 (differentiation) on CD4 and CD8 T cells, assessed using unstimulated whole blood which will be added to fluorochrome-conjugated antibodies that specifically detect the above mentioned factors. The percentage of positive cells is measured using flow cytometry at baseline, 6, 12 and 24 months after treatment onset

Assessment of safety:
Adverse events (AE) assessed and described in the scope of the daily observed treatment (DOT). This involves: a) occurrence of AE, b) intensity of AE (Grade 0 [none], Grade 1 [mild], grade 2 [moderate] grade 3 [severe], c) SAE, d) relation to treatment (definite, probable, possible, remote, not related), e) outcome of AE (restored, improved, unchanged, deteriorated, death, unknown, overcome with sequelae, f) intervention

Overall study start date
01/01/2017

Completion date
31/12/2025

Eligibility

Key inclusion criteria
1. Lymphedema of at least one leg grade 1-6 measured on a 7-point scale [3]
2. Age ≥ 14 years and ≤ 65 years
3. Men or non-pregnant women. If women of childbearing-potential, they must use an approved, effective method of contraception (including abstinence) before, during and for at least 2 weeks after the completion of the active intervention with doxycycline or placebo
4. Negative pregnancy test
5. Body weight ≥ 40 kg
6. Resident in LF endemic area for ≥ 2 years
7. Able and willing to give informed consent/ to provide assent to participate in the trial
8. Ability to use established standardized methods of hygiene and effectively applying it prior to the initiation of the drug treatment

Participant type(s)
Patient

Age group
Mixed

Sex
Both

Target number of participants
Group A (LE stage 1-3): n = 360, Group B (LE stage 4-6): n = 60

Total final enrolment
420

Key exclusion criteria
1. No lymphedema or lymphedema stage 7
2. Age < 14 years or > 65 years
3. Body weight < 40 kg
4. Pregnant or breastfeeding women
5. Women of childbearing potential not using an agreed method of contraception (including abstinence; oral contraceptives are not allowed because of interaction with trial drugs)
6. Clinical or biologic evidence of hepatic or renal dysfunction or disease of the central nervous system (CNS)
7. Evidence of severe comorbidities except for features of filarial disease
8. Alcohol or drug abuse
9. History of adverse reactions to doxycycline or other tetracyclines
10. Any significant condition (including medical and psychological/ psychiatric disorder) which in the opinion of the study investigator might interfere with the conduct of the study
11. History of photosensitivity reactions after taking drugs.
12. Concomitant medication with antacids containing aluminium, magnesium or sucralfate and not able to discontinue
13. Concomitant medication with other antibiotics than doxycycline and not able to discontinue
14. Concomitant medication with diuretics or sulfonylurea
15. Concomitant medication with coumarin
16. Haemoglobin < 8 gm/dL
17. Neutrophil count <2000/mm3 - updated 03/08/2018: Neutrophil count <1100/mm3
18. Platelet count <100,000/mm3
19. Creatinine > 2 times upper limit of normal
20. AST (GOT) > 2 times upper limit of normal
21. ALT (GPT) > 2 times upper limit of normal
22. Gamma-GT > 2 times upper limit of normal
23. Positive urine pregnancy test

Date of first enrolment
18/07/2018

Date of final enrolment
31/08/2025

Locations

Countries of recruitment
Tanzania

Study participating centre
The National Institute of Medical Research (NIMR)
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Sponsor information

Organisation
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Sponsor type
Research organisation

ROR
https://ror.org/05fjs7w98

Funder(s)

Funder type
Research organisation

Funder Name
Research Networks for Health Innovations in Sub-Saharan Africa sponsored by the Federal Ministry of Education and Research (BMBF)

Results and Publications

Publication and dissemination plan
The publication of the study results is planned in a high-impact peer reviewed journal.

Intention to publish date
31/07/2022

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study are not expected to be made available as consent was not provided for this.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol article	protocol	30/03/2020	02/04/2020	Yes	No
Results article		27/08/2024	03/12/2024	Yes	No