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Comparison of doxycycline alone versus doxycycline plus rifampicin in their efficacy against lymphatic filariasis

Submission date	Recruitment status	[_] Prospectively registered
19/03/2009	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
30/04/2009	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
20/11/2012	Infections and Infestations	[_] Record updated in last year

Plain English summary of protocol
Not provided at time of registration

Study website
http://www.a-wol.net/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number

Secondary identifying numbers
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Study information

Scientific Title
Comparison of doxycycline alone versus doxycycline plus rifampicin in their efficacy against lymphatic filariasis: a randomised, double-blind, placebo-controlled trial

Acronym
A-WOL LF

Study objectives
1. To refine existing regimes of drugs with known activity against Wolbachia (doxycycline, rifampicin):
1.1. To provide a shortened treatment period compared to the "gold-standard" (200 mg doxycycline per day for 4 weeks) using the combination of doxycycline and rifampicin
1.2. To provide a reduction of the daily dosage of doxycycline from 200 mg to 100 mg
2. To verify an ameliorating effect of doxycycline and the combination of doxycycline and rifampicin on the dilation of supratesticular lymphatic vessels (i.e. subclinical lymphatic pathology) using the different drug regimes

As of 01/12/2009 an additional follow-up timepoint after 18 months was approved by all three ethics committees for the secondary outcomes. Please see the secondary outcome measures section below for more details.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethical clearances have been obtained from the Committee on Human Research Publication and Ethics, Kwame Nkrumah University of Science and Technology, Kumasi, Ghana (approved 16th April 2008), from the Ethical Committee, University Clinic Bonn, Faculty of Medicine, Bonn, Germany (approved 18th March 2008) and from the Research Ethics Committee, Liverpool School of Tropical Medicine, Liverpool, UK (approved 26th March 2008).

Study design
Randomised double-blind placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Other

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
Lymphatic filariasis (Wuchereria bancrofti)

Interventions
The participants are randomised and assigned to one of the following seven treatment regimens:

Treatment regimen 1 (n = 65):
4 weeks doxycycline 200 mg followed by 1 week placebo matching doxycycline (2 capsules/day)
3 weeks placebo matching rifampicin (3 or 4 capsules)

Treatment regimen 2 (n = 39):
5 weeks doxycycline 100 mg (1 capsule/day)
5 weeks placebo matching doxycycline (1 capsule/day)
3 weeks placebo matching rifampicin (3 or 4 capsules)

Treatment regimen 3 (n = 39):
4 weeks doxycycline 100 mg followed by 1 week placebo matching doxycycline (1 capsule/day)
5 weeks placebo matching doxycycline (1 capsule/day)
3 weeks placebo matching rifampicin (3 or 4 capsules)

Treatment regimen 4 (n = 39):
3 weeks doxycycline 200 mg followed by 2 weeks placebo matching doxycycline (2 capsules/day)
3 weeks rifampicin (10 mg/kg BW, 3 or 4 capsules at 150 mg/day)

Treatment regimen 5 (n = 39):
2 weeks doxycycline 200 mg followed by 3 weeks placebo matching doxycycline (2 capsules/day)
2 weeks rifampicin (10 mg/kg BW) followed by 1 week placebo matching rifampicin (3 or 4 capsules/day)

Treatment regimen 6 (n = 39):
10 days doxycycline 200 mg followed by 25 days placebo matching doxycycline (2 capsules/day)
10 days rifampicin (10 mg/kg BW) followed by 11 days placebo matching rifampicin (3 or 4 capsules/day)

Treatment regimen 7 (n = 39):
5 weeks placebo matching doxycycline (2 capsules/day)
3 weeks placebo matching rifampicin (3 or 4 capsules/day)

The total duration of follow-up for all arms of our trial is 24 months after the start of drug administration.

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Intervention Type
Drug

Phase
Phase II/III

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

Primary outcome measure
Current primary outcome measures as of 08/11/2012 (protocol change approved by the DMEC of this trial on 02/03/2011, before de-blinding on 24/05/2011):
Macrofilaricidal effect of the different treatment arms verified as absence of worm nests (Filaria Dance sign [FDS]; adult filariae in dilated lymphatic vessels) in the supratesticular vessels detected by ultrasonography, assessed 12 months after the start of drug administration.

Previous primary outcome measures until 08/11/2012:
Macrofilaricidal effect of the different treatment arms assessed by reduction in the number of worm nests (Filaria Dance sign [FDS]; adult filariae in dilated lymphatic vessels) in the supratesticular vessels detected by ultrasonography, measured pre-treatment as well as 12 months after the start of drug administration.

For all above mentioned primary and secondary outcome measures: Treatment regimens 2 to 6 will subsequently be tested first for superiority compared to placebo (regimen 7) and second for equivalence to the standard therapy (regimen 1).

Secondary outcome measures
Current secondary outcome measures as of 08/11/2012 (protocol change approved by the DMEC of this trial on 02/03/2011, before de-blinding on 24/05/2011):
1. Macrofilaricidal effect of the different treatment arms verified as absence of FDS in the supratesticular vessels detected by ultrasonography, assessed 18 and 24 months after the start of drug administration
2. Macrofilaricidal effect of the different treatment arms assessed by reduction in the number of FDS in the supratesticular vessels detected by ultrasonography compared to pre-treatment, determined 12, 18 and 24 months after the start of drug administration

3. Macrofilaricidal effect of the different treatment arms assessed by reduction of circulating filarial antigen (CFA) levels compared to pre-treatment, measured by TropBio® ELISA and ICT card test 12, 18 and 24 months after the start of drug administration
4. Long-term sterilising effect of the female adult worms in the different treatment arms as assessed by microfilaria (mf) count (filtration method):
4.1 Reduction (%) or absence of microfilariae
4.2 Duration (months) of amicrofilaraemia
5. Reduction (%) or absence of Wolbachia ftsZ copy numbers/microfilariae compared to pre-treatment, assessed by polymerase chain reaction (PCR) 4, 12, 18 and 24 months after the start of drug administration
6. Reduction of supratesticular lymphatic vessel dilation compared to pre-treatment, measured 12, 18 and 24 months after the start of drug administration
7. Parasite specific immuno-globulin subclasses and cytokine responses, as well as other biomarkers such as vascular endothelial growth factors (VEGFs) measured pre-treatment as well as 4, 12 and 24 months after the start of drug administration

Previous secondary outcome measures as of 01/12/2009, until 08/11/2012:
1. Macrofilaricidal effect of the different treatment arms assessed by reduction in the number of worm nests in the supratesticular vessels detected by ultrasonography, measured 18 and 24 months after the start of drug administration
2. Macrofilaricidal effect of the different treatment arms assessed by absence of FDS in the supratesticular vessels detected by ultrasonography, measured pre-treatment as well as 12, 18 and 24 months after the start of drug administration
3. Macrofilaricidal effect of the different treatment arms assessed by levels of antigenaemia (enzyme-linked immunosorbent assay [ELISA] test) - reduction of circulating filarial antigen [CFA]) - measured pre-treatment as well as 4, 12, 18 and 24 months after the start of drug administration
4. Long-term sterilising effect of the female adult worms in the different treatment arms as assessed by microfilaria (mf) count (filtration method) and polymerase chain reaction (PCR) analysis:
4.1. Reduction (%) or absence of microfilariae
4.2. Duration (months) of amicrofilaraemia
4.3. Reduction (%) or absence of Wolbachia ftsZ copy numbers/microfilariae assessed by PCR
Measured pre-treatment as well as 4, 12, 18 and 24 months after the start of drug administration
5. Reduction of supratesticular lymphatic vessel dilation measured pre-treatment as well as 12, 18 and 24 months after the start of drug administration
6. Parasite specific immuno-globulin subclasses and cytokine responses, as well as other biomarkers such as vascular endothelial growth factors (VEGFs) measured pre-treatment as well as 4, 12, 18 and 24 months after the start of drug administration

For all above mentioned primary and secondary outcome measures: Treatment regimens 2 to 6 will subsequently be tested first for superiority compared to placebo (regimen 7) and second for equivalence to the standard therapy (regimen 1).

Initial information at time of registration:
1. Macrofilaricidal effect of the different treatment arms assessed by reduction in the number of worm nests in the supratesticular vessels detected by ultrasonography, measured 24 months after the start of drug administration
2. Macrofilaricidal effect of the different treatment arms assessed by absence of FDS in the supratesticular vessels detected by ultrasonography, measured pre-treatment as well as 12 and 24 months after the start of drug administration
3. Macrofilaricidal effect of the different treatment arms assessed by levels of antigenaemia

(enzyme-linked immunosorbent assay [ELISA] test) - reduction of circulating filarial antigen [CFA]) - measured pre-treatment as well as 4, 12 and 24 months after the start of drug administration
4. Long-term sterilising effect of the female adult worms in the different treatment arms as assessed by microfilaria (mf) count (filtration method) and polymerase chain reaction (PCR) analysis:
4.1. Reduction (%) or absence of microfilariae
4.2. Duration (months) of amicrofilaraemia
4.3. Reduction (%) or absence of Wolbachia ftsZ copy numbers/microfilariae assessed by PCR
Measured pre-treatment as well as 4, 12 and 24 months after the start of drug administration
5. Reduction of supratesticular lymphatic vessel dilation measured pre-treatment as well as 12 and 24 months after the start of drug administration
6. Parasite specific immuno-globulin subclasses and cytokine responses, as well as other biomarkers such as vascular endothelial growth factors (VEGFs) measured pre-treatment as well as 4, 12 and 24 months after the start of drug administration

For all above mentioned primary and secondary outcome measures: Treatment regimens 2 to 6 will subsequently be tested first for superiority compared to placebo (regimen 7) and second for equivalence to the standard therapy (regimen 1).

Overall study start date
01/05/2008

Completion date
30/04/2011

Eligibility

Key inclusion criteria
Current inclusion criteria as of 08/11/2012 (protocol change approved by the DMEC of this trial on 02/03/2011):
1. Men aged between 18 - 50 years
2. Good general health without any clinical condition requiring long-term medication and with normal renal and hepatic laboratory profiles
3. Body weight (BW): ≥40kg
4. Presence of at least one scrotal worm nest detected by ultrasonography

Previous inclusion criteria until 08/11/2012:
3. Body weight (BW): 40 - 70 kg

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Male

Target number of participants
299

Key exclusion criteria
1. Known intolerance to the study drugs (doxycycline, rifampicin), or to ivermectin and/or albendazole
2. History of severe allergic reaction or anaphylaxis
3. History of alcohol or drug abuse
4. Anti-filarial therapy within the last 10 months
5. Evidence of clinically significant neurological, cardiac, pulmonary, hepatic, metabolic, rheumatologic or renal disease as far as it can be assessed by history of participants, physical examination, and/or laboratory examinations including blood and urine analysis
6. Laboratory evidence of liver disease (alanine aminotransferase [ALT], gamma-glutamyl transferase [gamma-GT] greater than 1.25 times the upper limit of normal results as stated by the manufacturer of dipstick tests, Roche®)
7. Laboratory evidence of renal disease (serum creatinine greater than 1.25 times the upper limit of normal results as stated by the manufacturer of dipstick tests, Roche®)
8. Laboratory evidence of diabetes (urine dipstick chemistry)
9. Behavioural, cognitive or psychiatric disease that in the opinion of the trial clinician affects the ability of the participant to understand and comply with the study
10. Severe asthma or respiratory disease (emergency room visit or hospitalisation)
11. Undergone splenectomy
12. Participation in other drug trials concurrent with this study
13. 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
01/05/2008

Date of final enrolment
30/04/2011

Locations

Countries of recruitment
Germany

Ghana

Study participating centre
Institute of Medical Microbiology, Immunology and Parasitology
Bonn
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Sponsor information

Organisation
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Sponsor type
Hospital/treatment centre

Website
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ROR
https://ror.org/03svjbs84

Funder(s)

Funder type
Research organisation

Funder Name
Bill and Melinda Gates Foundation (USA) - via the Liverpool School of Tropical Medicine (UK)

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