Repeated Controlled Human Hookworm Infection in Healthy Dutch Volunteers

Published: 17-11-2017
Last updated: 13-04-2024

Primary objective:* To determine the safety and tolerability of repeated infection of Necator americanus L3 larvae in healthy volunteersSecondary objectives:* To compare the variability in egg output after cumulative infection with 50, 100 and 150...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Helminthic disorders
Study type	Interventional

Summary

ID

NL-OMON47227

Source
ToetsingOnline

Brief title
ReCHHI1

Condition

- Helminthic disorders

Synonym
Hookworm infection, parasitic infection

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum
Source(s) of monetary or material Support: Bioraphte

Intervention

Keyword: Hookworm, Infectious disease, Necator americanus, Tropical disease

Outcome measures

Primary outcome

Frequency and magnitude of adverse events as compared between study groups A, B and C.

Secondary outcome

Secondary endpoints

* Variability in egg secretion by Kato-Katz from week 16 to 20

* The lowest dose at which there is 100% patent hookworm infection, as defined by a positive Kato-Katz at any time between week 16 to 20

* Comparison of the average number of eggs secreted by Kato-Katz and qPCR between different groups in weeks 16-20 after the infection

* Humoral (antibody) and cellular immunological changes after controlled human hookworm infection.

Exploratory endpoints

* Changes in metabolomic profile in urine, serum, and faeces after CHHI

* Changes in gut microbiome after CHHI

* Time to positive faeces test for hookworm as defined by Kato-Katz and qPCR

* Changes in lactose/mannitol ratio and related biomarkers of intestinal permeability (i.e. serum zonulin, serum LPS) and intestinal inflammation (i.e. fecal calprotectin, serum diamine oxidase) after CHHI

Study description

Background summary

With over 700 million people infected worldwide, hookworm is one of the most common and the most important parasitic infection of humans. It largely affects the poor, causing iron-deficiency anaemia and hypoalbuminemia. Unfortunately, mass drug administration, the cornerstone of hookworm control programmes, is threatened by increasing drug failure and high reinfection rates. Novel anthelminthic drugs and vaccines are urgently needed to add to the hookworm control tools. Because there is no animal model for human hookworm infection, human studies are indispensable to screen novel drugs and vaccines for efficacy. Controlled human hookworm infection (CHHI) trials were initially developed as a model to assess the beneficial effects of hookworm infection on autoimmune diseases. For CHHI to be utilised as drug and vaccine testing platform, it has to be redesigned to reduce variability and establish consistent and quantifiable infection in all volunteers. This objective was not met in previous CHHIs, because egg output was always highly variable between individuals and timepoints. Consistent infection is a crucial criterium for every infection model so that the efficacy of an intervention can be confidently quantified. Previous trials showed that the highest tolerable dose so far, a single inoculation with 50 Necator americanus L3 larvae did not lead to persistent secretion of hookworm eggs in faecal samples. Incidental reports of higher doses (100 larvae) showed a decreased tolerability of the infection. Therefore, we now aim to perform multiple infections over time to maintain tolerability and increase total larval dose to attain consistent infection.

Study objective

Primary objective:
* To determine the safety and tolerability of repeated infection of Necator americanus L3 larvae in healthy volunteers

Secondary objectives:
* To compare the variability in egg output after cumulative infection with 50, 100 and 150 L3 Necator americanus larvae
* To explore the immunological changes following controlled hookworm infection.

Exploratory objectives:
* To explore changes in metabolomic profile of urine and serum and faeces after controlled hookworm infection
* To explore the changes in gut microbiome after hookworm infection
* To compare the diagnostic performance of microscopy and PCR to detect the presence of eggs in the faeces

* To explore changes in gut permeability after controlled hookworm infection

Study design

This study is a double-blind, placebo-controlled, dose-escalation trial.

Intervention

Twenty-four volunteers will be allocated equally into three groups (i.e. group A, B, C). Group A, B, and C will have one, two, and three infections respectively. Every infection will be performed with 50 L3 Necator americanus larvae. Group A will receive infection at week 4 only. Group B will be infected at week 2 and week 4. Group C will be infected at week 0, 2 and 4. To maintain blinding, group A and B will receive mock infections with water at week 0 and week 0 and 2 respectively. The interval between each CHHI is 2 weeks. Before every infection, the safety will be assessed by a review of adverse events data with a local safety monitor.
Sixteen weeks after the last infection (week 20), all volunteers will be offered treatment with a 3-day regimen of albendazole to abrogate infection. Volunteers with average egg counts >250 eggs per gram will be asked if they would be willing to keep their infection for a maximum of two years (chronic donors). No more than four volunteers will be selected to be chronic donors. Six months after the last infection (or after the last donation for the chronic donors) volunteers will undergo their last visit.

Study burden and risks

Burden: The number of follow-up visits is the same for all groups. Chronic donors will have more visits. Follow-up visits will be done weekly for 23 weeks. The amount of blood collected per volunteer will be 600 mL. Fecal samples will be taken weekly from week 0. Physical examinations will be performed when clinically indicated and subjects will be asked to complete a diary of adverse events on a daily basis.

Risks: Volunteers will be exposed to larval inoculum for up to three times. Risks for volunteers are related to i) penetration of N. americanus larvae through the skin and ii) systemic and local signs & symptoms of hookworm infection (eg. abdominal pain, nausea). After 20 weeks of follow-up, all participants are treated with albendazole. Clearance of infection is confirmed by faecal Kato-Katz and qPCR.

Benefits: There are no direct benefits for volunteers.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Subject is aged * 18 and * 45 years and in good health.
2. Subject has adequate understanding of the procedures of the study and agrees to abide strictly thereby.
3. Subject is able to communicate well with the investigator, is available to attend all study visits.
4. Subject agrees to refrain from blood donation to Sanquin or for other purposes throughout the study period.
5. For female subjects: subject agrees to use adequate contraception and not to breastfeed for the duration of study.
6. Subject has signed informed consent.

Exclusion criteria

1. Any history, or evidence at screening, of clinically significant symptoms, physical signs or abnormal laboratory values suggestive of systemic conditions, such as cardiovascular, pulmonary, renal, hepatic, neurological, dermatological, endocrine, malignant, haematological, infectious, immune-deficient, psychiatric and other disorders, which could compromise the health of the volunteer during the study or interfere with the interpretation of the study results. These include, but are not limited to, any of the following:
* Body Mass Index (BMI) <18.0 or >35.0 kg/m2 at screening;
* positive HIV, HBV or HCV screening tests;
* the use of immune modifying drugs within three months prior to study onset (inhaled and topical corticosteroids and oral anti-histamines exempted) or expected use of such during the study period;
* Having one of the following laboratory abnormalities: ferritine <10ug/L, transferrine <2.04g/L or Hb <7.0 mmol/L for females or <8.0 mmol/L for males.
* history of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years;
* any history of treatment for severe psychiatric disease by a psychiatrist in the past year;
* history of drug or alcohol abuse interfering with normal social function in the period of one year prior to study onset.
2. Known hypersensitivity to or contra-indications for use of albendazole. Including co-medication known to interact with albendazole metabolism (e.g. carbamazepine, phenobarbital, phenytoin, cimetidine, theophylline, dexamethasone)
3. Known allergy to amphotericin B or gentamicin.
4. For female subjects: positive urine pregnancy test at screening.
5. Positive faecal qPCR or Kato-Katz for hookworm at screening, any known history of hookworm infection or treatment for hookworm infection or possible exposure to hookworm in the past.
6. Being an employee or student of the department of parasitology of the LUMC.
7. Current or past scars, tattoos, or other disruptions of skin integrity at the intended site of larval application.
8. Subjects with planned travel to hookworm endemic areas during this trial
9. Receipt of a vaccine within 4 weeks prior to the study initiation
10. Known food allergy

Study design

Design

Study type: Interventional

Masking:	Double blinded (masking used)
Control:	Uncontrolled

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-01-2018
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO

Date:	17-11-2017
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Approved WMO

Date:	21-02-2018
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT03257072
CCMO	NL59186.058.17

Study results

Date completed:	04-09-2018
Results posted:	09-01-2020
Actual enrolment:	24

First publication
19-09-2019