Safety and protective efficacy of repeated controlled human Schistosoma mansoni Infection

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Primary Objectives: - To determine the protective efficacy of repeated exposure to male Schistosoma mansoni (Sm) cercariae in healthy Schistosome-naïve volunteers based on CAA levels.- To determine the safety and tolerability of repeated exposure to...

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

Summary

ID

NL-OMON50894

Source
ToetsingOnline

Brief title
ReCoHSI

Condition

- Helminthic disorders

Synonym
bilharzia, Schistosomiasis

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Infectious disease, Schistosoma mansoni, Schistosomiasis, Tropical medicine

Outcome measures

Primary outcome

- The protective efficacy of repeated exposure to male Sm cercariae measured by the difference in frequency of serum CAA positivity (>=1.0 pg/mL) between the reinfection group and the infection control group at any timepoint after the final infection at week 18;

- Frequency and severity of adverse events after (repeated) human Sm infection with male cercariae

Secondary outcome

Exploratory endpoints:

- Comparison of time to positive serum and urine CAA test between the reinfection and infection control groups after the final infection at week 18;

- Comparison of peak serum CAA concentration between the reinfection and infection control group after the final infection at week 18;

- Comparison of eosinophil counts between the reinfection and infection control groups after challenge after the final infection at week 18;

- Comparison of (glycan) antibody responses directed against Sm antigens between the reinfection and infection control participants as well as between protected and non-protected participants after the final infection at week 18 using protein and glycan arrays;

- Comparison of cellular responses directed against Sm antigens between the reinfection and infection control participants as well as between protected and

non-protected participants after the final infection at week 18 using flow

cytometry;

- The pooled attack rate after initial exposure to 20 male cercariae, i.e.

proportion CAA positivity between week 0-8 for the reinfection participants and

between week 18-26 for infection control participants.

Study description

Background summary

Schistosomiasis is a parasitic disease of global importance that affects around 140 million people mainly living in (sub)tropical regions. The development of a vaccine against schistosomiasis has been hampered by limited research funding as well as knowledge gaps relating to how (natural) immunity against schistosomiasis develops. Epidemiological data suggests that natural immunity develops in an age- and IgE-dependent manner. Moreover, animal experiments in mice and non-human primates provide the strongest evidence that development of protective immunity is feasible: in animals immunised with radiation attenuated (RA) cercariae worm burden reduction up to 80% were observed. Protection was associated with upregulated Th1 polarized CD4+ cells and increased IgG, but not IgE antibodies. At the LUMC, we recently developed a controlled human Schistosoma mansoni infection (CoHSI) model using single-sex cercariae that do not produce eggs and therefore prevents egg-associated morbidity in study participants. Infection with 20 male cercariae was safe and well-tolerated. The immune responses following infection showed a predominant Th1 skewing coupled with increases of worm-specific IgG and IgG1, but not IgE. The use of this model is not only limited to testing of vaccine candidates, but can also provide a unique opportunity to investigate immune responses after repeated exposure to cercariae and to establish whether this leads to protective immunity in humans. Based on the comparable immune responses after CoHSI in humans and RA immunisation in mice and non-human primates, we hypothesize that repeated exposure to male cercariae results in protection to reinfection. As such, correlates of protection may also be identified that improve our understanding of immunity, as well as also lead to the discovery of new vaccine targets.

Study objective

Primary Objectives:
- To determine the protective efficacy of repeated exposure to male Schistosoma

mansoni (Sm) cercariae in healthy Schistosome-naïve volunteers based on CAA levels.
- To determine the safety and tolerability of repeated exposure to male Sm cercariae;

Exploratory Objectives:
- To investigate the kinetics of circulating anodic antigen (CAA) after repeated exposure to male Sm cercariae;
- To explore potential differences in immunological responses and CAA kinetics between single-exposure vs. repeated-exposure to male Sm cercariae;
- To investigate immunological markers associated with protection against Schistosoma mansoni infection.

Study design

Double-blind, placebo-controlled randomised trial.

Intervention

24 volunteers will be randomised in a 1:1 ratio to the intervention group and the control group. The intervention group (i.e. reinfection group) will be exposed three times to 20 male Sm cercariae (weeks 0,9, 18) whereas the control group (i.e. infection control group) will only be exposed once (week 18). This group will receive a mock infection with water on weeks 0 and 9. Participants in the intervention group will be treated with praziquantel at weeks 8,17, and 30 to cure infection, while the control group will receive placebo treatment at weeks 8 and 17, followed by praziquantel treatment at week 30.

Study burden and risks

Volunteers will visit the trial centre for screening, then at one day prior to infection, at the day of infection and every other week until the next infection. On the weeks in between, follow up visits will be conducted per email/phone. After the final infection (from week 20 onwards), participants will visit the study centre weekly up until week 30. After week 30, follow-ups will take place every two weeks until week 38, with in-between phone visits at weeks 31 and 33. Final visit will be performed at week 54. In total there are 27 regular visits, 3 infection days, and 11 phone visits. At all follow up visits, adverse events will be recorded, volunteers will undergo a blood draw by venepuncture and will provide a urine sample. At some visits, nasosorption samples are collected. They will keep a diary to record adverse events for 38 weeks. Volunteers will be dermally exposed to male cercariae once or three times, depending on the randomisation group. They may experience adverse events, such as cercarial dermatitis or symptoms related to acute schistosomiasis syndrome with fatigue, malaise, and fever. It is unclear

whether repeated infections lead to increased risk of developing symptoms of acute schistosomiasis or whether this risk decreases with increasing number of infections. Data from endemic settings suggest the latter, since symptoms of acute schistosomiasis are not frequently reported. At weeks 8, 17 and 30, those in the reinfection group will be treated with praziquantel to cure the Schistosoma infection. Participants in the infection control group are treated with praziquantel at week 30. Praziquantel is known to potentially give fatigue, gastrointestinal side effects, and dizziness. There is no benefit to participation in the trial.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

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 will remain within Europe (excluding Corsica) during the study period.
5. Subject agrees to refrain from blood and plasma donation to Sanquin or for other purposes throughout the study period.
6. For female subjects: subject agrees to use adequate contraception and not to breastfeed for the duration of study.
7. 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, (severe) 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 weight <50 kg or 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;
- 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. The chronic use of any drug known to interact with praziquantel, artesunate or lumefantrine metabolism (e.g. phenytoïn, carbamazepine, phenobarbital, primidon, dexamethason, rifampicine, cimetidine, flecaïnide, metoprolol, imipramine, amitriptyline, clomipramine, class IA and III anti-arrythmics, antipsychotics, antidepressants, macrolides, fluorchinolones, imidazole- and triazole antimycotics, antihistamines). Because lumefantrine may cause extension of QT-time, chronic use of drugs with effect on QT interval will result in exclusion from study participation.
3. For female subjects: positive urine pregnancy test at screening.
4. Any history of schistosomiasis or treatment for schistosomiasis.
5. Positive serology for schistosomiasis or elevated serum CAA at screening.
6. Known hypersensitivity to or contra-indications (including co-medication)

for use of praziquantel, artesunate or lumefantrine.
7. Being an employee or student of the department of Parasitology or Infectious diseases of the LUMC.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	29-10-2021
Enrollment:	24
Type:	Actual

Ethics review

Approved WMO

Date:	13-10-2021
Application type:	First submission
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
CCMO	NL77749.058.21
Other	volgt

Study results

Results posted: 04-01-2024

First publication
02-01-2024