Immunological and Genetic Risk factors for Cardiac Serious Adverse Events following Controlled Human Malaria Infections: a Case-Control study

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To identify host risk factors through genetic and immunological screening that may be associated with the development of cardiac SAEs following CHMI. Identification of such factors may on the one hand allow at-risk individuals to be screened out…

Ethical review	Not approved
Status	Will not start
Health condition type	Cardiac disorders, signs and symptoms NEC
Study type	Observational invasive

Summary

ID

NL-OMON50610

Source
ToetsingOnline

Brief title
Risk factors for cardiac SAEs following CHMI

Condition

- Cardiac disorders, signs and symptoms NEC

Synonym
Myocarditis (inflammation of the heart muscle) and acute coronary syndrome (range of conditions associated with sudden, reduced blood flow to the heart)

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Cardiac SAEs, Case-control study, Controlled Human Malaria Infection, Immunogenetic predisposition

Outcome measures

Primary outcome

1. Immunological risk factors with significant odds ratios for cardiac SAEs

following CHMI, i.e. in cases compared to controls.

2. Genetic factors/deviations/variants identified in one or more cases which

can (possibly and/or partially) explain why these subjects suffered cardiac

SAEs following CHMI.

Secondary outcome

1. Immunological factors/deviations/variants identified in one or more cases

which can (possibly and/or partially) explain why these subjects suffered

cardiac SAEs following CHMI.

Study description

Background summary

Malaria, a disease caused by Plasmodium parasites, is one of the most important infectious diseases worldwide. After a period of relative success in global malaria control, progress has stalled since 2015. Resistance to medication is increasing in endemic areas and a fully efficacious vaccine has still not been developed. Controlled Human Malaria Infections (CHMI), a model in which study participants are infected with Plasmodium parasites in a controlled (research) setting, are an important and established tool in malaria research, especially in the clinical development of malaria vaccines. CHMI is considered a

reproducible, predictable and safe model and has been performed successfully at Radboudumc since 1998 in over 500 individuals, resulting in paradigm-shifting developments such as CPS immunisation. Nevertheless, since 2002 five of these subjects developed a cardiac Serious Adverse Event (acute coronary syndrome, often resembling myocarditis) following CHMI at Radboudumc. Cardiac SAEs have never been described in thousands of participants at other CHMI centres worldwide, nor after the hundreds of millions of cases of uncomplicated natural malaria infection that occur each year. Despite inclusion of stricter in- and exclusion criteria and additional safety controls to subsequent protocols after each respective event, SAEs have continued to occur sporadically and a clear cause remains to be identified, although the presentation and timing of these SAEs suggest a (delayed) abnormal inflammatory response may play a role. Additional investigation into possible causes is therefore desirable with a view to further improving safety, either by modifying the overall model or by excluding at-risk participants. In addition to factors that may be unique to the CHMI model at Radboudumc, we hypothesize that some subjects are predisposed (through either genetic background or prior immunological history) to an abnormal inflammatory reaction following CHMI, leading to these adverse events.

Study objective

To identify host risk factors through genetic and immunological screening that may be associated with the development of cardiac SAEs following CHMI. Identification of such factors may on the one hand allow at-risk individuals to be screened out prior to inclusion and/or suggest modifications to the overall CHMI in future studies.

Study design

A case-control study; cases and controls are defined in the section 'Study population'. Cases and controls will be invited for a first study visit, including medical history, physical examination, blood samples for routine lab tests and immunological screening and a urine sample for drug screening. Consent to request medical files from general practitioners will be asked. If cases consent to this, they will additionally undergo genetic screening (Whole Exome Sequencing (WES)), under supervision of a clinical geneticist. All subjects will be invited for a final study visit. One or max. a couple of extra study visits inc. blood sampling for immunological tests may be necessary, depending on the initial results.

Study burden and risks

At least two study visits for all study participants, with a total duration of approximately 1.5 hours. Cases have the possibility to undergo genetic analysis, which consists of two consultations with a clinical geneticist and holds the risk of incidental findings. Venous blood samples will be taken at

least once for controls, and at least twice for cases undergoing genetic screening. No direct health benefit of participation is expected for either cases or controls, but insight gained should help to improve the safety of CHMI studies, which in themselves are a markedly valuable tool in the global fight against malaria.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study as a case, a subject must meet all of the following criteria:
1. Subject must sign written informed consent to participate in the trial.
2. By judgement of the clinical investigator, the subject is able to understand the planned study procedures and (limited) risks associated with the study, inc. the risk of incidental findings in genetic analysis.

3. The subject was enrolled in a CHMI study performed by the Radboudumc between January 1998 and December 2021 and was subjected to a Controlled Human Malaria Infection. Subject developed a cardiac serious adverse event in the period of 20 days following CHMI. A cardiac SAE is defined as either clinically significant increased troponin levels and/or diagnosis of myocarditis, acute coronary syndrome or myocardial infarction by a cardiologist, and meet the criteria of an SAE as defined in the study protocol.
4. Subjects unwilling and/or unable to participate in genetic analysis, are still eligible for immunological analysis (and vice versa).

In order to be eligible to participate in this study as a control, a subject must meet all of the following criteria:
1. The subject has signed written informed consent.
2. The subject is able to understand the study procedures and (limited) risks associated with the study.
3. The subject was enrolled in a CHMI study performed by the Radboudumc between January 1998 and December 2021 and was subjected to a Controlled Human Malaria Infection. Subject did not develop a cardiac serious adverse event in the period of 20 days following CHMI. A cardiac SAE is defined as either clinically significant increased troponin levels and/or diagnosis of myocarditis, acute coronary syndrome or myocardial infarction by a cardiologist, and meets the criteria of an SAE as defined in the respective study protocol.

Exclusion criteria

A potential case or control subject who meets any of the following criteria will be excluded from participation in immunological screening:
1. Subject is HIV-positive or suffers from any other (acute or chronic) disease as determined by medical history, physical examination or laboratory screening tests which according to the clinical judgment of the investigator leads to undesirable interference with the results of the immunological tests. The clinical investigator will consider whether blood samples without such interference can be obtained later in the study period (e.g. in case of acute infectious disease).
2. Use or receipt of
i) immunosuppressive drugs or other immune modifying drugs within three months prior to blood sampling for immunological screening (inhaled and topical corticosteroids and oral anti-histamines exempted) OR
ii) use of illicit drugs determined through urine drug screening OR
iii) any vaccinations within 30 days prior to immunology blood sampling
IF use of these drugs or receipt of a vaccination lead to undesirable interference with the results of the immunological tests according to the clinical judgment of the investigator. The clinical investigator will consider whether blood samples without such interference can be obtained later in the

study period.
3. Any history of malaria other than CHMI as part of the Radboudumc trial in which the subject has previously participated.

A potential case subject who meets any of the following criteria will be excluded from participation in genetic analysis:
1. A history of bone marrow transplantation.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	25
Type:	Anticipated

Ethics review

Not approved

Date:	24-03-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

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
Other	Clinicaltrials.gov (nog te registreren)
CCMO	NL79934.091.21