Immunization with Plasmodium falciparum sporozoites under chloroquine versus mefloquine prophylaxis

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Primary Objective: To compare protection against controlled Plasmodium falciparum malaria infection after immunization with sporozoites under chloroquine with immunization under mefloquine prophylaxis. Secondary Objectives: • To study and compare...

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

Summary

ID

NL-OMON35200

Source
ToetsingOnline

Brief title
ZonMw2

Condition

- Protozoal infectious disorders

Synonym
Malaria, Plasmodium falciparum

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: ZonMw

Intervention

Keyword: chloroquine, malaria, mefloquine, plasmodium falciparum

Outcome measures

Primary outcome

Duration of prepatent period after challenge infection as measured by

microscopy

Secondary outcome

Parasitemia and kinetics of parasitemia as measured by PCR

Frequency of signs or symptoms in study groups

Immune responses between in study groups

Study description

Background summary

Malaria is one of the major infectious diseases in the world with a tremendous impact on the quality of life, significantly contributing to the ongoing poverty in endemic countries. It causes 800.000 deaths per year, the majority of which are children under the age of five. The malaria parasite enters the human body through the skin, by the bite of an infected mosquito. Subsequently, it invades the liver and develops and multiplies inside the hepatocytes. After a week, the hepatocytes burst open and the parasites are released in the blood stream, causing the clinical phase of the disease.
As a unique opportunity to study malaria immunology and efficacy of immunisation strategies, a protocol has been developed in the past to conduct controlled human malaria infections (CHMIs). CHMIs generally involve small groups of malaria-naïve volunteers infected via the bites of P. falciparum infected laboratory-reared Anopheline mosquitoes. Although potentially serious or even lethal, P. falciparum malaria can be radically cured at the earliest stages of blood infection when risks of complications are virtually absent.
We have shown previously that healthy human volunteers can be protected from a malaria mosquito (sporozoite) challenge by immunization with sporozoites (by mosquito bites) under chloroquine prophylaxis (CPS immunization). Interestingly, sterile protection in 100% of the human CPS immunized volunteers was achieved by a relatively miniscule dose, i.e. a total of 45 infectious

mosquito bites, strikingly 20-fold more potent than the 1000 bites needed in a model using irradiated mosquitoes.One possible explanation for this efficiency is contribution of the known immune modulating effects of chloroquine to the induction of protective immunity. We aim to assess this possible immune modulating effect in CPS immunization by comparing immunization with P. falciparum sporozoites under chloroquine with immunization under mefloquine prophylaxis, which has the same antimalarial effect, but not the immune modulating effects known from chloroquine.

Study objective

Primary Objective: To compare protection against controlled Plasmodium falciparum malaria infection after immunization with sporozoites under chloroquine with immunization under mefloquine prophylaxis.

Secondary Objectives:
• To study and compare development of parasitemia after challenge between study groups
• To analyze and compare the immune responses between study groups

Study design

Single centre, double-blind randomized controlled clinical trial\

Intervention

The study population will be randomly divided in three groups. For a period of 16 weeks, Group 1 (n=5) will receive chloroquine prophylaxis, Group 2 (n=10) and 3 (n=5) will receive mefloquine prophylaxis.
In this period, all volunteers will be exposed to mosquito-bites at days 22, 50 and 78. Group 1 and 2 will receive Plasmodium falciparum infected mosquito-bites, Group 3 will receive uninfected mosquito-bites.
Sixteen weeks after discontinuation of prophylaxis, all volunteers will be challenged by the bites of five P. falciparum infected mosquitoes. After challenge, all volunteers will be treated with a curative regimen of Malarone® (each tablet containing 250 mg atovaquone and 100 mg proguanil).

Study burden and risks

Benefits: No benefit can be claimed for any of the volunteers. Even though immunized volunteers might be protected to P. falciparum from the challenge in this study, these effects may not apply to field situations. Therefore, volunteers will be advised to take regular malaria prophylaxis when travelling to malaria endemic areas in the future.

Risks: Risks for volunteers are related to exposure to (early) P. falciparum

malaria infection and side-effects of chloroquine or mefloquine prophylaxis and Malarone® treatment.

Burden: The study is associated with an immunization period of three months in which the volunteers receive immunization with mosquito bites in every first week of the month, and make a visit to the trial centre five times in the second week. During these three months, they have to take weekly prophylaxis, either chloroquine or mefloquine. After the challenge there will be a short period (35 days) of intense clinical monitoring with frequent site visits and blood examinations. As it is unpredictable if and/or when subjects will develop a positive thick blood smear after challenge infection, it is impossible to state the exact number of site visits and blood examinations. However, the maximum number (in case a subject does not develop a positive blood smear) of site visits and blood examinations will be 65 with a maximum amount of collected blood of 1000 mL. In addition periodical physical examinations will be performed and the subject is asked to complete a diary.

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. Age >= 18 and <= 35 years healthy volunteers (males or females)
2. Good health based on history and clinical examination
3. Negative pregnancy test
4. Use of adequate contraception for females
5. Signing of the informed consent form, thereby demonstrating understanding of the meaning and procedures of the study
6. Agreement to inform the general practitioner and to sign a request to release medical information concerning contra-indications for participation in the study
7. Willingness to undergo a Pf controlled infection through mosquito bites
8. Agreement to stay in a hotel room close to the trial center during a part of the study (Day 5 after challenge till treatment is finished)
9. Reachable (24/7) by mobile phone during the whole study period
10. Available to attend all study visits
11. Agreement to refrain from blood donation to Sanquin or for other purposes, during the whole study period
12. Willingness to undergo HIV, hepatitis B and hepatitis C tests
13. Negative urine toxicology screening test at screening visit and the day before challenge
14. Willingness to take a prophylactic regime of chloroquine or mefloquine and curative regimen of Malarone®

Exclusion criteria

1. History of malaria
2. Plans to travel to malaria endemic areas during the study period
3. Plans to travel outside of the Netherlands during the challenge period
4. Previous participation in any malaria vaccine study and/or positive serology for Pf
5. Symptoms, physical signs and laboratory values suggestive of systemic disorders including renal, hepatic, cardiovascular, pulmonary, skin, immunodeficiency, psychiatric, and other conditions which could interfere with the interpretation of the study results or compromise the health of the volunteers
6. History of diabetes mellitus or cancer (except basal cell carcinoma of the skin)
7. History of arrhythmias or prolonged QT-interval
8. Positive family history in 1st and 2nd degree relatives for cardiac events < 50 years old
9. An estimated, ten year risk of fatal cardiovascular disease of >=5%, as estimated by the Systematic Coronary Risk Evaluation (SCORE) system
10. Clinically significant abnormalities in electrocardiogram (ECG) at screening
11. Body Mass Index (BMI) below 20 or above 30 kg/m2
12. Any clinically significant deviation from the normal range in biochemistry or hematology

blood tests or in urine analysis
13. Positive HIV, HBV or HCV tests
14. Participation in any other clinical study within 30 days prior to the onset of the study
15. Enrollment in any other clinical study during the study period
16. For women: pregnancy or lactation
17. Volunteers unable to give written informed consent
18. Volunteers unable to be closely followed for social, geographic or psychological reasons
19. History of drug or alcohol abuse interfering with normal social function
20. A history of treatment for psychiatric disease or moderate or severe psychological episode in volunteer
21. A history of convulsions in volunteer
22. Severe depression, anxiety disorder of psychosis in first or second degree family
23. Contra-indications to Malarone®, chloroquine or mefloquine including hypersensitivity or treatment taken by the volunteer that interferes with Malarone®, chloroquine or mefloquine
24. The use of chronic immunosuppressive drugs, antibiotics, or other immune modifying drugs within three months of study onset (inhaled and topical corticosteroids and oral anti-histaminic are allowed) and during the study period
25. Any confirmed or suspected immunosuppressive or immunodeficient condition, including asplenia
26. Co-workers or trainees of the departments of Medical Microbiology, Parasitology, or Internal Medicine of the Leiden University medical Centre
27. A history of sickle cell anemia, sickle cell trait, thalassemia, thalassemia trait or G6PD deficiency

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-04-2012
Enrollment:	20

Type:	Actual

Ethics review

Approved WMO Date:	19-12-2011
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	12-06-2012
Application type:	Amendment
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
CCMO	NL37563.058.11
Other	volgt