Re-exposure of previously immunized and challenged human volunteers to a heterologous strain of P. falciparum sporozoites

Published: 03-07-2012
Last updated: 26-04-2024

To determine protective immunity against a heterologous P. falciparum sporozoites re-challenge after previous CPS immunization and challenge.

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

Summary

ID

NL-OMON37778

Source
ToetsingOnline

Brief title
TIP4

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: TI Pharma

Intervention

Keyword: heterologous, Malaria, plasmodium falciparum, re-challenge

Outcome measures

Primary outcome

Primary Objective: To determine protective immunity against a heterologous P.

falciparum sporozoites re-challenge after previous CPS immunization and

challenge.

Secondary outcome

Secondary endpoints:

• Parasitemia and kinetics of parasitemia as measured by PCR

• Frequency of signs or symptoms in study groups

• Immune responses between study groups

Study description

Background summary

Malaria is one of the major infectious diseases in the world with a tremendous impact on quality of life, significantly contributing to the ongoing poverty in endemic countries. It causes approximately 655.000 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, develops and multiplies inside hepatocytes. After approximately one week, the hepatocytes burst open and parasites are released in the blood stream, leading to the clinical phase of the disease.

As a unique opportunity to study malaria immunology and efficacy of immunisation strategies, a protocol has been developed to conduct controlled human malaria infections (CHMIs). CHMIs are studies consisting of a small group of malaria-naïve volunteers who are infected through bites of infected (e.g. Plasmodium. falciparum) laboratory-reared Anopheles 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 and symptoms are usually mild.
We have shown previously that healthy human volunteers can be protected from a P. falciparum challenge by immunization with sporozoites (by mosquito bites) under chloroquine prophylaxis (CPS immunization). Interestingly, sterile protection in nearly all human CPS immunized volunteers was achieved by a relatively low dose, i.e. a total of 45 infectious mosquito bites.

In the ZonMw1 study (NL33904.091.10), we challenged a total of 24 volunteers after CPS immunization of three groups with 45, 30 or 15 infected mosquito-bites respectively. Seventeen of 24 these volunteers were fully protected against a homologous challenge after CPS immunization while 7 volunteers developed parasitaemia with a similar prepatent period as the control group. The availability of this immunized cohort opens the unique opportunity to determine protection to a heterologous challenge for both of the protected and unprotected volunteers as the previous challenge infection might have served as an immunological boost to the unprotected volunteers.

We therefore aim to investigate through an observational, proof of principle, study to assess the protection on an individual basis of all previously immunized and challenged volunteers against a heterologous P. falciparum NF135.C10 challenge.

Study objective

To determine protective immunity against a heterologous P. falciparum sporozoites re-challenge after previous CPS immunization and challenge.

Study design

The study is a single centre open label clinical trial. Laboratory personnel will be blinded, volunteers and the investigators will both not be blinded.

A maximum of 25 volunteers will be divided into two groups as shown in Table 1. All volunteers will be challenged by the bites of 5 mosquitoes, infected with the P. falciparum NF135.C10 strain.

Table 1
1. n=20; Immunized subjects ZonMw1
2. n=5; control group

Intervention

All volunteers will be exposed to five P. falciparum NF135.C10 infected mosquito-bites.

Study burden and risks

Benefits: No benefit can be claimed for any of the volunteers. Even though previously immunized and challenged volunteers (ZonMw1) might be protected to P. falciparum in this study, these effects may not apply to field situations. Therefore, volunteers will be advised to take adequate malaria prophylaxis and preventative measurements (e.g. bednet, deet etc) 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 Malarone® treatment. Volunteers will be given the results of the screeningstests (HBV, HCV, HIV, pregnancy test and tox screen).

Burden: Volunteers have to fill in a health questionnaire before screening. Approximately 10 days before malaria infection (challenge) volunteers will undergo leukapheresis at Sanquin bloodbank accoding to standard operating procedures and is located close tot the study centre . By means of a needle in the forearm PBMCs will be filtered during approximately 30 minutes in order to study immune responses against malaria. The burden for the volunteer is minimal, sometimes temporarily tingling sensations can be experienced in lips or fingers and disappear readily after drinking calcium-containing drinks (e.g. milk) or taking calcium tablets The challenge infection, in which volunteers receive mosquito bites, will take place on day 0, and volunteers have to make visits to the trial centre in the 140 days afterwards, starting on day 5 after challenge. After challenge there will be a period (35 days) of intense clinical monitoring with frequent site visits and blood examinations. The first two days involve once daily visits. The next nine days will involve twice daily visits, the six days afterwards once a day. After start of Malarone treatment, volunteers visit the trial centre twice a day. 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 will be 39 (34 blood examinations) with a maximum amount of collected blood of 500 mL . In addition periodical physical examinations will be performed and the subject is asked to complete a diary and measure temperature orally.

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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 challenge through mosquito bites
8. Agreement to stay in a hotel room close to the trial centre 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 curative regimen of Malarone®
15. Adequate venous access for leukapheresis

Exclusion criteria

1. History of malaria (other than participation in ZonMw1 study) or residence in malaria endemic areas within the past six months
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 (except ZonMw1 volunteers)
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 18 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: being pregnant or lactating
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
21. A history of convulsions
22. Contra-indications to Malarone®, including hypersensitivity or treatment taken by the volunteer that interferes with Malarone®
23. 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
24. Any confirmed or suspected immunosuppressive or immunodeficient condition, including (functional) asplenia
25. Co-workers or trainees of the departments Infectious Diseases, Medical Microbiology or Parasitology of the Leiden University Medical Centre (LUMC) or Medical Microbiology, Parasitology, Radboud University Nijmegen (RUNMC)
26. A history of sickle cell anaemia, sickle cell trait, thalassaemia (or trait), G6PD deficiency

Study design

Design

Study type:	Interventional
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	27-08-2012
Enrollment:	29
Type:	Actual

Ethics review

Approved WMO

Date:	03-07-2012
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
CCMO	NL39414.000.12
Other	volgt