Identification of pre-erythrocytic target antigens induced by Plasmodium falciparum sporozoite immunization under chemoprophylaxis.

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Primary objective: To delineate the antibody repertoire directed against the pre-erythrocytic stages of Plasmodium falciparum induced by CPS-immunization.Secondary objectives: • To assess the functionality of CPS-immunization induced antibodies.• To...

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

Summary

ID

NL-OMON40673

Source
ToetsingOnline

Brief title
BMGF1

Condition

- Protozoal infectious disorders

Synonym
malaria, Plasmodium falciparum

Research involving
Human

Sponsors and support

Primary sponsor: Radboud universitair medisch centrum

Source(s) of monetary or material Support: Bill and Melinda Gates Foundation

Intervention

Keyword: antigens, immunity, malaria, vaccine

Outcome measures

Primary outcome

Generation of B-cells for delineation of antibody responses against Plasmodium falciparum pre-erythrocytic stages in CPS-immunized, protected volunteers.

Secondary outcome

1. Functionality of CPS-immunization induced antibodies for protection against pre-erythrocytic stages of Plasmodium falciparum.

2. The specificity of CPS-immunization induced T-cell responses against pre-erythrocytic stages of Plasmodium falciparum.

Study description

Background summary

Malaria, a disease caused by the parasite Plasmodium, is one of the world*s major infectious diseases. With approximately 627.000 deaths a year, it is both a chief cause of morbidity and mortality as well as a significant contribution to ongoing poverty in endemic countries. Ultimately, the key to malaria control and hopefully eradication, would be an effective vaccine. Though a number of vaccine-candidates have entered the pipeline of pre-clinical and clinical development, they have yet to achieve the level of efficacy necessary for effective malaria prevention. It has been shown previously that healthy human volunteers can be fully protected against malaria infection with a homologous parasite by immunization with Plasmodium parasites while taking chloroquine chemoprophylaxis (ChemoProphylaxis and Sporozoites, CPS-immunization). The unprecedented efficacy of CPS-immunization makes it a unique model to identify target antigens for the development of a subunit vaccine. Identification of antigens that play a significant role in the development of sterile protection against malaria will provide a basis for the development and evaluation of more

effective sub-unit candidate vaccines.

Study objective

Primary objective:
To delineate the antibody repertoire directed against the pre-erythrocytic stages of Plasmodium falciparum induced by CPS-immunization.

Secondary objectives:
• To assess the functionality of CPS-immunization induced antibodies.
• To determine T-cell antigen specificities in CPS-immunized, protected volunteers.

Exploratory objectives:
• To assess the functionality of CPS-immunization induced T-cells.
• To explore the adaptive and innate immune responses during CPS-immunization and early malaria infection.

Study design

This is a single-centre, randomized open-label study. A total of 15 volunteers will be divided into two groups, one scheduled to receive CPS immunization (Group 1, n=10) and one to receive only chloroquine prior to malaria challenge (Group 2, n=5).

Intervention

In the immunization group a total of four CPS immunizations will be performed, with 15 bites from Plasmodium infected mosquitoes per immunization, over a period of four months, during which volunteers will take chloroquine prophylaxes. The control group will take only chloroquine prophylaxes during this period. All volunteers will undergo CHMI by exposure to 5 bites from Plasmodium falciparum sporozoite infected mosquitoes.

Study burden and risks

For patients assigned to the immunization group the study is associated with several short periods of intense clinical monitoring with frequent site visits (up to two times a day) and blood examinations. For patients assigned to the control group intensive monitoring is limited to once during a period of two to four weeks. As it is unpredictable when subjects will develop a positive qPCR or thick blood smear, 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 qPCR or blood smear) of site visits and blood examinations in the immunization group will be 70. In both groups the maximum amount of collected blood over the period of 8 months will be 1200 mL. In addition

immunization group will undergo leukapheresis twice and in both groups 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

- Subject is aged >= 18 and <= 35 years and in good health.
- Subject has adequate understanding of the procedures of the study and agrees to abide strictly thereby.
- Subject is able to communicate well with the investigator, is available to attend all study visits, lives in proximity to the trial centre (<10 km) or (if >10km) is willing to stay in a hotel close to the trial centre during part of the study (day 5 post-infection until three days post-treatment). Furthermore the subject will remain within the Netherlands during the challenge

period, not travel to a malaria-endemic area during the study period, and is reachable (24/7) by mobile telephone throughout the entire study period.
- Subject agrees to inform his/her general practitioner about participation in the study and to sign a request to release by the GP any relevant medical information concerning possible contra-indications for participation in the study.
- Subject agrees to refrain from blood donation to Sanquin or for other purposes throughout the study period and for a defined period thereafter according to current Sanquin guidelines.
- For female subjects: subject agrees to use adequate contraception and not to breastfeed for the duration of study.
- Subject has signed informed consent.;Additional inclusion criteria (as added by Amendment 2 - 05-Dec-2014 on trial day 61)
- Subject agrees to refrain from intensive physical exercise (disproportionate to the subjects usual daily activity or exercise routine) for ten days following each immunization and during the malaria challenge period.

Exclusion criteria

- Any history, or evidence at screening, of clinically significant symptoms, physical signs or abnormal laboratory values suggestive of systemic conditions, or psychiatric disorders, which could compromise the health of the volunteer during the study or interfere with the interpretation of the study results.
- Body weight <50 kg or Body Mass Index (BMI) <18.0 or >30.0 kg/m2 at screening
-A heightened risk of cardiovascular disease, as determined by: an estimated ten year risk of fatal cardiovascular disease of >=5% at screening, as determined by the Systematic Coronary Risk Evaluation (SCORE); history, or evidence at screening, of clinically significant arrhythmia*s, prolonged QT-interval or other clinically relevant ECG abnormalities; or a positive family history of cardiac events in 1st or 2nd degree relatives <50 years old.
- Medical history of functional asplenia, sickle cell trait/disease, thalassaemia trait/disease or G6PD deficiency.
- History of epilepsy in the period of five years prior to study onset, even if no longer on medication.
- Positive HIV, HBV or HCV screening tests.
- Chronic use of i) immunosuppressive drugs, ii) antibiotics, iii) or other 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, or positive urine toxicology test for cocaine or amphetamines at screening or prior to infection.
- For female subjects: positive urine pregnancy test at screening or prior to infection.
- Any history of malaria, positive serology for P. falciparum, or previous participation in any malaria (vaccine) study.
- Known hypersensitivity to or contra-indications (including co-medication) for use of

chloroquine, Malarone or artemether-lumefantrine, or history of severe (allergic) reactions to mosquito bites.
- Receipt of any vaccinations in the 3 months prior to the start of the study or plans to receive any other vaccinations during the study period or up to 8 weeks thereafter.
- Participation in any other clinical study in the 30 days prior to the start of the study or during the study period.
- Being an employee or student of the department of Medical Microbiology of the Radboudumc or the department of Internal Medicine.
- Any other condition or situation that would, in the opinion of the investigator, place the subject at an unacceptable risk of injury or render the subject unable to meet the requirements of the protocol.;Additional exclusion criteria (as added by Amendment 2 - 05-Dec-2014 on trial day 61)
- Positive urine toxicology test for cannabis at inclusion or prior to infection.

Study design

Design

Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	03-10-2014
Enrollment:	15
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	11-06-2014
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	02-10-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	08-12-2014
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	26-03-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	30-04-2015
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-11-2015
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
ClinicalTrials.gov	NCT02080026
CCMO	NL48301.091.14