Controlled Human Malaria Infection after bites from mosquitoes infected with NF135.C10 or NF166.C8 Plasmodium falciparum parasites

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Primary Objective: To assess the proportion of volunteers who develop parasitemia after Controlled Human Malaria Infection with bites from one, two or five NF166.C8- or NF135.C10-infected mosquitoes.Secondary Objectives: To assess kinetics of...

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

Summary

ID

NL-OMON40942

Source
ToetsingOnline

Brief title
BMGF2a

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: Bill and Melinda Gates Foundation

Intervention

Keyword: malaria, Plasmodium falciparum

Outcome measures

Primary outcome

Proportion of subjects developing patent parasitaemia after CHMI

Secondary outcome

Kinetics of parasitaemia in subjects after CHMI, e.g. pre-patent period and

height of first peak, as assessed by qPCR

Frequency and severity of adverse events

Study description

Background summary

Rationale: Plasmodium falciparum malaria remains responsible for an intolerable burden of morbidity worldwide and an effective vaccine is sorely needed to aid control efforts. Before candidate malaria vaccines can enter full-scale (phase IIb) field trials in endemic areas, they must first be tested under controlled circumstances in (phase IIa) controlled human malaria infection studies. Since 1998 a highly successful Controlled Human Malaria Infection model at the UMC St Radboud has been employed both to test candidate vaccines and to answer fundamental questions about pathophysiological and immunological mechanisms during early Pf infection in human volunteers.
Since Pf isolates display a wide genetic diversity across the globe, phase IIa challenge infections should be conducted with both homologous and heterologous strains. To date largely the NF54 strain of P. falciparum has been used in this Nijmegen model, with which extensive experience has meanwhile been acquired. In order to increase the portfolio of Pf strains available for future phase IIa studies, the parasitological and clinical characteristics of the new candidate strains NF135.C10 and NF166.C8 were recently compared to those of NF54 in a controlled human malaria infection (TIP3 study, NL41004.078.12). This study demonstrated that, when all infections were induced as usual with 5 infective mosquito bites, both candidate strains produced higher liver-stage loads (and thus earlier patent parasitaemia) than the well-charecterised NF54 strain,

without eliciting a more fulminant clinical course.
The main aim of the current study is therefore to determine whether the two new P. falciparum strains also reliably induce infections with fewer mosquito bites per volunteer. Due to their lower parasite load, such infection are conceivably even better tolerated by the volunteers and their dynamics more comparable to NF54's in future heterologous challenge studies.
For the sub-study "Odour profile" a collaboration has again been entered into with the department of (medical) entomology of the University Wageningen, where research is performed into the attractiveness of malaria patients for mosquitoes. By determining the chemicals responsible for this, odour traps may be designed in the future to distract mosquitoes in endemic areas in order to reduce transmission. The goal of the current sub-study is to recapitulate in a larger number of subjects the findings from earlier pilot sub-studies.

Study objective

Primary Objective: To assess the proportion of volunteers who develop parasitemia after Controlled Human Malaria Infection with bites from one, two or five NF166.C8- or NF135.C10-infected mosquitoes.
Secondary Objectives: To assess kinetics of parasitaemia and clinical parameters following CHMI with bites from one, two or five NF166.C8- or NF135.C10-infected mosquitoes
Exploratory objectives: To explore the (innate) immunology of early malaria infection. To explore (patho)physiological aspects of early malaria infection. To construct a personalized health curve model of tolerance and resistance to early P. falciparum infection. To evaluate the Quantitative Buffy Coat technique for the detection of parasitaemia in early malaria infection. To explore the attractiveness of volunteers* odour profile to mosquitoes during early malaria infection in the sub-study *Odour profile*.

Study design

single centre, dubble blind, randomised

Intervention

Twenty four healthy volunteers will be randomised double-blindly to six groups each consisting of 4 volunteers. Group 1 will be exposed to the bites of five mosquitoes infected with the NF135.C10 strain of Plasmodium falciparum; Group 2 will be exposed to two NF135.C10-infected mosquitoes and 3 uninfected mosquitoes; Group 3 will be exposed to one NF135.C10-infected mosquito and four uninfected mosquitoes; Group 4 will be exposed to five NF166.C8-infected mosquitoes; Group 5 will be exposed to two NF166.C8-infected mosquitoes and 3 uninfected mosquitoes; Group 6 will be exposed to one NF166.C8-infected mosquito and four uninfected mosquitoes. Following exposure, all volunteers who live >10km from the Havenziekenhuis will be required to stay in a study hotel

in the vicinity of the Havenziekenhuis from day 5 post infection until 3 days after treatment, for safety reasons. All volunteers will (at some point during the study) be treated with a curative regimen of Malarone® (atovaquon/proguanil): 4 tablets of 250/100mg qd for three days, according to Dutch national *Stichting Werkgroep Antibiotica Beleid* (SWAB) guidelines.
Criteria for initiation of treatment in an individual volunteer are as follows:
1. Two consecutive positive qPCR results in a volunteer with temperature <38.0C
2. One positive qPCR result in a volunteer with temperature >=38.0C
3. One positive thick blood smear
4. By decision of study doctor or the safety monitor
5. On request of the volunteer
6. On day 13 post CHMI, if the volunteer has remained qPCR-negative
7. When hs Troponine T (Roche) is > 0.1 µg/mL (=100,000 ng/L) or on recommendation of the cardiologist
8. When thrombocytes < 120 x 10^9/L
9. When LDH > 1000 U/l
In case of participation in the sub-study "Odour profile", the odour of volunteers will also be collected on 3-4 occasions (D-2, D6, D8* and D34) by non-invasive methods. *Unless already on anti-malarial treatment.

Study burden and risks

Benefits: No benefit can be claimed for any of the volunteers. It is not to be expected that volunteers will develop protective immunity against malaria following infection. 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 Malarone® treatment.
Burden: The study is associated with a short period (35 days) of intense clinical monitoring with frequent site visits (twice a day) and daily blood examinations. As it is unpredictable when subjects will develop a positive qPCR, it is impossible to state the exact number of site visits and blood examinations. However, the maximum number of visits and blood examinations (in case a subject does not develop a positive qPCR by day 13) will be 25 with a maximum amount of collected blood of 500 mL. In addition physical examinations will be performed as necessary and
the subject is asked to complete a diary of symptoms. During part of the study (day 5 until three days after treatment) volunteers who live >10km from the Havenziekenhuis are required to stay overnight in a hotel near the Havenziekenhuis for safety reasons.
In case of participation in the sub-study "Odour profile" furthermore: 2 additional visits to the Havenziekenhuis and compliance with the behavioural rules (not showering for 24 hours three/four times during the study).

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. Subject is aged >= 18 and <= 35 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 and 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 study period and is reachable (24/7) by mobile telephone throughout the entire study period.
4. 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.
5. 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.
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, immunodeficient, 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:
1.1 Body weight <50 kg or Body Mass Index (BMI) <18.0 or >30.0 kg/m2 at screening
1.2 A heightened risk of cardiovascular disease, defined as: 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.
1.3 Functional asplenia, sickle cell trait/disease, thalassaemia trait/disease or G6PD deficiency.
1.4 History of epilepsy in the period of five years prior to study onset, even if no longer on medication.
1.5 Positive HIV, HBV or HCV screening tests.
1.6 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.
1.7 History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years
1.8 Any history of treatment for severe psychiatric disease by a psychiatrist in the past year.
1.9 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.
2. For female subjects: positive urine pregnancy test at screening or prior to infection.
3. Any history of malaria, positive serology for P. falciparum, or previous participation in any malaria (vaccine) study.
4. Known hypersensitivity to or contra-indications (including co-medication) for use of atovaquone-proguanil (Malarone) or artemether-lumefantrine (Riamet), or history of severe (allergic) reactions to mosquito bites.
5. Receipt of any vaccinations in the 3 months prior to the start of the study or plans to receive any vaccinations during the study period or up to 8 weeks thereafter.
6. Participation in any other clinical study in the 30 days prior to the start of the study or during the study period.
7. Being an employee or student of the department of Medical Microbiology of the Radboudumc, the department of Internal Medicine or Laboratory of the Havenziekenhuis or

the department of Medical Microbiology & Infectious Diseases of the Erasmus MC.
8. 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.

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):	07-10-2014
Enrollment:	24
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	16-07-2014
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
ClinicalTrials.gov	NCTnrvolgt
CCMO	NL48704.000.14