Comparison of three Plasmodium falciparum isolates in a controlled human malaria infection

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Primary objective (parasitological): To investigate the parasitaemic kinetics of three different Plasmodium falciparum isolates (NF54, NF135 and NF166) during a controlled human malaria infection.Secondary objective (parasitological, clinical and...

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

Summary

ID

NL-OMON37044

Source
ToetsingOnline

Brief title
TIP3

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: Top Institute Pharma

Intervention

Keyword: malaria, Plasmodium falciparum

Outcome measures

Primary outcome

A significant difference in the kinetics of parasitemia between infections with

NF54, NF135 en NF166

Secondary outcome

A significant difference in time to thick smear positivity between infections

with NF54, NF135 en NF166

A significant difference in the duration and peak height of parasitemia as

measured by PCR between infections with NF54, NF135 en NF166

A significant difference in the incidence of symptoms in volunteers infected

with NF54, NF135 and NF166

A significant difference in immunological response (serological or cellular) in

volunteers infected with NF54, NF135 and NF166

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 Pf isolates display a wide genetic diversity across the globe, phase IIa challenge infections should be conducted with both homologous and heterologous strains.
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. 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, it is first necessary to document in detail the parasitological, clinical and immunological characteristics of new candidate strains during a controlled human malaria infection. In this study, the strains NF135 and NF166 will be compared in this regard with the well-charecterised NF54 strain.
For the sub-study "Odour profile" a collaboration has 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.

Study objective

Primary objective (parasitological): To investigate the parasitaemic kinetics of three different Plasmodium falciparum isolates (NF54, NF135 and NF166) during a controlled human malaria infection.
Secondary objective (parasitological, clinical and immunological): To investigate additional parasitological, clinical and immunological characteristics of these three Plasmodium falciparum isolates during infection.
Exploratory objectives (immunological, pathophysiological and diagnostic): To explore the (innate) immunology of early malaria infection, with specific attention to gene expression profiles in circulating monocytes. To explore (biomarkers correlated with) vasopressin release during early malaria infection. To explore the value of different clinical diagnostic tools in the detection of parasistaemia in early malaria infection. Sub-study "Odour profile": to explore the attractiveness of volunteers to malaria mosquitoes before, during and after infection and analyse the chemicals and/or skin flora responsible for this.

Study design

single centre, dubble blind, randomised

Intervention

Fifteen healthy volunteers will be randomised double-blindly to three groups each consisting of 5 volunteers. The first group will be exposed to the bites of five mosquitoes infected with the NF54 strain of Plasmodium falciparum. The second group will be exposed to bites of 5 mosquitoes infected with the NF135 strain. The third group will be exposed to the bites of 5 mosquitoes infected with the NF166 strain. Following exposure, all volunteers 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:
• Positive thick blood smear during regular check-ups, with or without complaints of malarial infection
• Upon complaints of malarial infection and the extra thick blood smear is positive
• By decision of clinical investigator or the safety monitor
• On request of the volunteer
• On day 21 post-challenge, if the volunteer has remained thick blood smear negative until then
• If hs troponine T (Roche) > 0.1 µg/ml and on recommendation of the cardiologist
• If thrombocytes < 75 x 109/l
• Depending on abnormal values for LDH, D-dimer, ADAMTS13 and fragmentocytes (see also section 6.4)

In case of participation in the sub-study "Odour profile", the odour of volunteers will also be collected on three occasions (D-2, D7 en D34) by non-invasive methods.

Study burden and risks

Benefits: No benefit can be claimed for any of the volunteers. It is not to beexpected that volunteers will develop protective immunity against malaria following infection. Therefore, volunteers will be advised to take regular malaria prophylaxis when travelling to malaria endemie 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 thick blood smear, 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 blood smear by day 21) will be 35 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 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 thrice 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. Males and females aged 18-35 years
2. In general good health based on history, physical examination and basic haematology and biochemistry
3. Negative pregnancy test for females
4. Use of adequate contraception for females
5. Signed informed consent, based on a thorough understanding of the concept and procedures of the study

6. Volunteer agrees to allow informing his/her general practitioner about participation and agrees to sign a request for medical information from the GP concerning any contra-indications for participation in the study
7. Willingness to undergo a Pf sporozoite challenge
8. Agreement to stay in a hotel close to the trial center during part of the study (day 5 until three days post-treatment)
9. Reachable (24/7) by mobile telephone 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 course of the study and thereafter following Sanquin guidelines.
12. Willingness to undergo an HIV, HBV and HCV screening test
13. Negative urine toxicology screening test at the screening visit and on the day before challenge
14. Willingness to take a curative regimen of Malarone®

Exclusion criteria

1. History of malaria
2. Plans to travel outside of the Netherlands during the study period
3. Previous participation in any malaria vaccine study and/or positive serology for P. falciparum
4. Symptoms, physical signs or laboratory values suggestive of systemic disorders, including but not limited to renal, hepatic, cardiovascular, pulmonary, skin, immunodeficiency, psychiatric and other conditions, which could compromise the health of the volunteer during the study or interfere with the interpretation of the study results
5. History of diabetes mellitus or cancer (except basal cell carcinoma of the skin)
6. Clinically significant ECG abnormalities at screening, or history of arrhythmia*s or prolonged QT-interval
7. Positive family history of cardiac disease in 1st or 2nd degree relatives < 50 years old
8. An estimated ten year risk of fatal cardiovascular disease of >=5%, as estimated by the Systematic Coronary Risk Evaluation (SCORE) system
9. Body Mass Index (BMI) below 18 or above 30 kg/m2
10. Any clinically significant deviation from the normal range in haematological or biochemical blood tests or urine analysis
11. Positive HIV, HBV or HCV screening tests
12. Participation in any other clinical study within 30 days prior to the onset of the study or during the study period
13. Pregnant or lactating women
14. Volunteers unable to give written informed consent
15. Volunteers unable to be closely followed during the study period for social, geographic or psychological reasons
16. Previous history of drug or alcohol abuse interfering with normal social function in the period of one year prior to study onset
17. A history of psychiatric disease or convulsions
18. Known hypersensitivity to anti-malarial drugs

19. History of severe reactions or allergy to mosquito bites
20. The use of chronic immunosuppressive drugs, antibiotics, or other immune modifying drugs within three months prior to study onset (inhaled and topical corticosteroids are allowed) or during the study period
21. Contra-indications for Malarone® use, including treatment taken by the volunteers that interferes with Malarone®
22. Any confirmed or suspected immunosuppressive or immunodeficient condition, including asplenia
23. Co-workers of the departments of Medical Microbiology of the UMC St Radboud, the department of Internal Medicine of the Havenziekenhuis or the department of Medical Microbiology & Infectious Diseases of the Erasmus MC
24. A history of sickle cell, thalasaemia trait or G6PD deficiency ;For sub-study "Odour profile" additionally:
25. Smokers
26. Regular medicine use

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):	20-09-2012
Enrollment:	15
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO Date:	14-08-2012
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	21-09-2012
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
ClinicalTrials.gov	NCT01627951
CCMO	NL41004.078.12