Comparison of three Plasmodium falciparum isolates in an experimental human malaria infection

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• Primary objective (parasitological): To investigate the kinetics of parasitemia of different Plasmodium falciparum isolates• Secondary objective (immunological): To investigate parasite development and immunological properties of different...

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

Summary

ID

NL-OMON34733

Source
ToetsingOnline

Brief title
TIP1

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 kinetics of parasitemia between groups A, B and C.

Secondary outcome

• Mean time to thick smear positivity in groups A, B and C

• Mean duration of parasitemia and peak height of parasitemia as measured by

PCR in groups A, B and C

• Mean frequency of signs or symptoms in groups A, B and C

• Significant differences in antibody production between

groups A, B and C

• Significant differences in cellular immune response between groups A, B and C

• Significant differences in memory cytokine profile between groups A, B and C

Study description

Background summary

Rationale: Plasmodium falciparum isolates display a wide genetic diversity with possibly different properties to induce immune responses. These properties could directly influence the ability to induce protective efficacy. Since 1998 an experimental human malaria infection model at the Radboud University Nijmegen Medical Center (RUNMC) has been very successful in answering questions with regards to immunological mechanisms of human Pf infection. To date only the NF54 strain of Pf has been deployed in this Nijmegen model. However, investigation of heterologous Pf challenge is not only highly informative for our basic understanding of induction of immune responses but also provides an essential model for protective capacity testing in the clinical development of candidate malaria vaccines. Recently, the parasite culture laboratory of the RUNMC has been able to overcome technical hurdles to produce infectious

mosquitoes of two genetically different isolates from different geographical regions to increase the portfolio for Phase IIa trials. These isolates, PfA and PfB will be compared with the NF54 strain for parasitic, immunological and clinical features in humans.

Study objective

• Primary objective (parasitological): To investigate the kinetics of parasitemia of different Plasmodium falciparum isolates
• Secondary objective (immunological): To investigate parasite development and immunological properties of different Plasmodium falciparum isolates
• Exploratory objectives : To explore the pathophysiology of early malaria infection, with specific attention to immunological responses, iron metabolism and VAR gene expression.

Study design

single center, double blind, randomized

Intervention

All volunteers are exposed to the bites of 5 Plasmodium falciparum infected mosquitoes. All volunteers will be treated similarly after infection.

Fifteen healthy volunteers are randomised double blind to groups A, B and C, each consisting of 5 volunteers. Group A is exposed to the bites of five infectious mosquitoes infected with the PfA strain of Plasmodium falciparum. Group B is exposed to bites of mosquitoes infected with the PfB strain. Group C, the control group, is exposed to NF54 infected mosquitoes. Following exposure, volunteers are required to stay in the study hotel from day 5 post infection until 3 days after treatment. All volunteers will be treated with a curative regimen of Malarone® (atovaquon/proguanil); once daily 4 tablets of 250/100mg during three days, according to *Stichting Werkgroep Antibiotica Beleid* (SWAB) guidelines.
Criteria for treatment are as follows:
• Positive thick blood smear during regular check-up
• Complaints of malarial infection and positive thick blood smear
• By decision of study doctor or the safety monitor
• On request of the volunteer
• On day 21 post challenge, if the volunteer has remained thick blood smear negative
• When hs Troponine T (Roche) > 0.1 µg/ml and on recommendation of the cardiologist
• When thrombocytes < 75 x 109/l
• Dependent on abnormal values for LDH, D-dimer, ADAMTS13 and fragmentocytes

Study burden and risks

Benefits: No benefit can be claimed for any of the volunteers. Even though volunteers might be protected to patent blood-stage P. falciparum in this re-challenge, 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 Malarone® treatment.
Burden: The study is associated with a short period (35 days) of intense clinical monitoring with frequent site visits (up to three times a day) and 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 (in case a subject does not develop a positive blood smear) of site visits and blood examinations will be 43 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.

Contacts

Public
Universitair Medisch Centrum Sint Radboud

Postbus 9101
6500 HB Nijmegen
NL
Scientific
Universitair Medisch Centrum Sint Radboud

Postbus 9101
6500 HB Nijmegen
NL

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. General good health based on history and clinical examination
3. Negative pregnancy test
4. Use of adequate contraception for females
5. All volunteers have to sign the informed consent form following proper understanding of the meaning and procedures of the study
6. Volunteer agrees to inform the general practitioner and agrees to sign a request for medical information concerning contra-indications for participation in the study
7. Willingness to undergo a Pf sporozoite challenge
8. Agreement to stay in a hotel room close to the trial center during a part of the study (Day 5 till Day T +3)
9. Reachable 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 course of the study
12. Willingness to undergo an HIV, hepatitis B and C test
13. Negative urine toxicology screening test at screening visit and day before challenge
14. Willingness to take a curative regimen of Malarone®

Exclusion criteria

1. History of malaria
2. Plans to travel to endemic malaria areas during the study period
3. Plans to travel outside of the Netherlands during day 0-28 of the study
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 arrhythmia*s or prolonged QT-interval
8. Positive family history in 1st and 2nd degree relatives for cardiac disease < 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. Body Mass Index (BMI) below 18 or above 30 kg/m2
11. Any clinically significant deviation from the normal range in biochemistry or haematology

blood tests or in urine analysis
12. Positive HIV, HBV or HCV tests
13. Participation in any other clinical study within 30 days prior to the onset of the study
14. Volunteers enrolled in any other clinical study during the study period
15. Pregnant or lactating women
16. Volunteers unable to give written informed consent
17. Volunteers unable to be closely followed for social, geographic or psychological reasons
18. Previous history of drug or alcohol abuse interfering with normal social function during a period of one year prior to enrolment in the study
19. A history of psychiatric disease
20. Known hypersensitivity for anti-malaria drugs
21. History of severe reactions or allergy to mosquito bites
22. The use of chronic immunosuppressive drugs, antibiotics, or other immune modifying drugs within three months before study onset (inhaled and topical corticosteroids are allowed) and during the study period
23. Contra-indications to Malarone® including treatment taken by the volunteers that interfere with Malarone®
24. Any confirmed or suspected immunosuppressive or immunodeficiency condition, including asplenia
25. Co-workers of the departments of Medical Microbiology or Internal Medicine of the Radboud University Nijmegen Medical Centre or Leiden University Medical Center
26. A history of sickle cell, thalasaemia trait and 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:	Recruiting
Start date (anticipated):	19-04-2010
Enrollment:	15

Type:	Actual

Ethics review

Approved WMO Date:	11-03-2010
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	19-04-2010
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	NCT01002833
CCMO	NL30350.058.09