Experimental human malaria infection by intradermal injection of Plasmodium falciparum sporozoites (PfSPZ Challenge)

Published: 12-10-2010
Last updated: 03-05-2024

• Primary objective: To achieve a 100% infection rate of human volunteers by intradermal injection of aseptic, purified, cryopreserved Pf sporozoites (PfSPZ Challenge). • Secondary objective: To compare parasite kinetics between different doses of...

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

Summary

ID

NL-OMON35056

Source
ToetsingOnline

Brief title
TIP2

Condition

- Protozoal infectious disorders

Synonym
Malaria

Research involving
Human

Sponsors and support

Primary sponsor: Sanaria Inc., Stephen L. Hoffman, M.D.
Source(s) of monetary or material Support: Top Institute Pharma

Intervention

Keyword: Falciparum, Malaria, Plasmodium, Sporozoite

Outcome measures

Primary outcome

• 100% thick smear positivity of all volunteers from one group

Secondary outcome

• A significant difference in time of thick smear positivity between the groups of volunteers

• A significant quantitative difference in parasitemia as measured by retrospective RTQ-PCR between the groups of volunteers

• A significant difference in kinetics of parasitemia between the groups of volunteers as measured by retrospective RTQ-PCR.

• A difference in occurrence and/or intensity of signs or symptoms between the groups of volunteers

Study description

Background summary

Experimental human malaria infections are generally accepted to be a powerful tool for evaluation of potential malaria vaccine and drug efficacies. Until now, experimental infections have been performed exclusively using infectious mosquitoes. Recently, Sanaria has been able to overcome the technical issues associated with the production of aseptic, purified, cryopreserved Plasmodium falciparum (Pf) sporozoites (PfSPZ). Performing experimental human malaria infections with aseptic, purified, cryopreserved sporozoites clearly provides advantages over infectious mosquitoes, in terms of dose determination and standardisation and overcoming batch differences when performing sequential clinical trials. This trial is designed to find the dose of aseptic, purified, cryopreserved sporozoites (PfSPZ Challenge) that should be used for

experimental human malaria infections.

Study objective

• Primary objective: To achieve a 100% infection rate of human volunteers by intradermal injection of aseptic, purified, cryopreserved Pf sporozoites (PfSPZ Challenge).
• Secondary objective: To compare parasite kinetics between different doses of intradermal injection of PfSPZ Challenge.
• Tertiary objective: To compare immune responses in volunteers experimentally infected by different doses of intradermally injected PfSPZ Challenge.
• Exploratory objectives: To explore the pathophysiology of early malaria, with specific attention to coagulation, endothelial activation, complement activation and VAR gene expression.

Study design

single center, open label, with varying doses.

Intervention

Groups of 6 volunteers will be intradermally injected with PfSPZ Challenge. Groups will be injected 21 days apart. Three different doses of PfSPZ Challenge will be administered according to the scheme below.

Criteria for treatment with a curative regimen of Malarone® (each tablet containing 250 mg atovaquone and 100 mg proguanil) are as follows:
• Positive thick smear during regular check-up
• Symptoms consistent with malaria and positive thick 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 smear negative
• When hs Troponine T (Roche) > 0.1 µg/ml and on recommendation of the cardiologist
• When thrombocytes < 75 x 109/l
• Depending on abnormal values for LDH, D-dimer, ADAMTS13 and fragmentocytes
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Dosing will be as follows: once daily 4 tablets of Malarone® (each tablet containing 250 mg atovaquone and 100 mg proguanil), during three days, according to SWAB guidelines. Volunteers will be checked for parasites by thick smear at least twice after treatment.

Study burden and risks

Benefits: No benefit can be claimed for any of the volunteers. Volunteers will

be advised to take regular malaria prophylaxis when traveling to malaria endemic areas in the future.
Risks: Risks for volunteers are related to exposure to (early) P. falciparum malaria 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 if and/or when subjects will develop a positive thick 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 blood collected being 500 mL. In addition periodic physical examinations will be performed and the subject will be 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

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. All volunteers must sign the informed consent form demonstrating their understanding of the meaning and procedures of the study
6. Volunteer agrees to inform the general practitioner and agrees to sign a request to release medical information concerning contra-indications for participation in the study
7. Willingness to undergo a Pf sporozoite challenge
8. For volunteers not living in Nijmegen: agreement to stay in a hotel room close to the trial center during a part of the study (Day 5 till 3 days after treatment)
9. Reachable (24/7) by mobile phone during the whole study period
10. Living with a third party that could contact the clinicians in case of alteration of consciousness or agreement to stay in a hotel room close to the trial center during a part of the study (Day 5 till 3 days after treatment)
11. Available to attend all study visits
12. Agreement to refrain from blood donation to Sanquin or for other purposes, during the study period until day 140.
13. Willingness to undergo HIV, hepatitis B and hepatitis C tests
14. Negative urine toxicology screening test at screening visit and day before challenge
15. Willingness to take a curative regimen of Malarone®

Exclusion criteria

1. History of malaria
2. Plans to travel to malaria endemic areas during the 140 day 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 arrhythmias 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. 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. Pregnant or lactating women
17. Volunteers unable to give written informed consent
18. Volunteers unable to be closely followed for social, geographic or psychological reasons
19. Previous history of drug or alcohol abuse interfering with normal social function during a period of one year prior to enrolment in the study
20. A history of psychiatric disease
21. Known hypersensitivity to anti-malaria drugs
22. The use of chronic immunosuppressive drugs, antibiotics, or other immune modifying drugs within three months of study onset (inhaled and topical corticosteroids are allowed) and during the study period
23. Contra-indications to Malarone® including treatment taken by the volunteer that interferes with Malarone®
24. Any confirmed or suspected immunosuppressive or immunodeficient condition, including asplenia
25. Co-workers of the departments of Medical Microbiology or Internal Medicine of the Radboud University Nijmegen Medical Centre or Sanaria Inc.
26. A history of sickle cell anemia, sickle cell trait, thallasemia, thallasemia trait or G6PD deficiency

Study design

Design

Study type: Interventional

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-10-2010
Enrollment:	18
Type:	Actual

Ethics review

Not available

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
EudraCT	EUCTR2010-019300-23-NL
ClinicalTrials.gov	NCT01086917
CCMO	NL31858.091.10