Controlled Human Malaria Infection study to assess gametocytaemia and mosquito transmissibility in participants challenged with Plasmodium falciparum by sporozoite challenge to establish a model for the evaluation of transmission-blocking interventions

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Primary objectives:1) To evaluate the safety of CHMI-trans protocols in healthy malaria-naïve volunteers challenged with Plasmodium falciparum by sporozoite challenge and blood stage challenge. 2) To assess gametocyte infectiousness for Anopheles...

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

Summary

ID

NL-OMON44291

Source
ToetsingOnline

Brief title
CHMI-trans2

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: Path-MVI

Intervention

Keyword: malaria, gametocytes, Plasmodium falciparum, transmission

Outcome measures

Primary outcome

Primary endpoints:

* Frequency and magnitude of adverse events in the CHMI-trans model in study groups.

* Prevalence of gametocytes and gametocyte infectiousness for Anopheles mosquitoes through mosquito feeding assay (Direct Membrane Feeding Assay, DMFA) in study groups.

Secondary outcome

Secondary endpoints:

* Peak density and time-point of peak density of gametocytes by qRT-PCR.

* The area under the curve of gametocyte density versus time.

* Assessment of the dynamics of gametocyte commitment, maturation and sex-ratio.

* Prevalence of gametocyte infectiousness for Anopheles mosquitoes through Direct Feeding Assays (Direct Skin Feeding Assay, DFA) in study groups.

Study description

Background summary

Malaria is one of the most devastating infectious diseases worldwide. Despite all the progress that has been made in reducing the malaria burden, in 2013 there were still ~200 million cases and ~0.6 million deaths, mainly in children less than five years of age[1]. In addition to the intolerable clinical burden, malaria forms a profound economic burden for the affected countries, which are already struggling with poverty. The urgency of the situation is further emphasized by the waning effectiveness of all currently registered anti-malarials due to fast emergence and spread of resistance and the absence of an highly effective vaccine[2].
Malaria transmission blocking vaccines (TBVs) and transmission-blocking drugs aim to interrupt the development of parasites in the mosquito[3]. TBVs will play a central role in efforts to reduce the malaria burden, to contain drug resistance and to move towards malaria elimination[2, 4].
The clinical development of such transmission blocking interventions will be greatly accelerated by a suitable model for their evaluation.
Controlled Human Malaria Infections (CHMI) are an established model for evaluation of malaria candidate vaccines and drugs targeting pre-erythrocytic or asexual blood stages.
The primary aim of this project is to develop a controlled human malaria infection transmission model (*CHMI-trans*) or *challenge model* to evaluate the capacity of vaccines, biologics (monoclonal antibodies, or mAbs), and drugs to block malaria parasite transmission by assessing infectiousness of Plasmodium falciparum (Pf) gametocyte carriers for Anopheles mosquitoes.

Study objective

Primary objectives:
1) To evaluate the safety of CHMI-trans protocols in healthy malaria-naïve volunteers challenged with Plasmodium falciparum by sporozoite challenge and blood stage challenge.
2) To assess gametocyte infectiousness for Anopheles mosquitoes through mosquito feeding assay (Direct Membrane Feeding Assay, DMFA).

Secondary objectives:
3) To determine the dynamics of gametocyte commitment, maturation and sex ratio by molecular markers of sexual stage development.
4) To determine the time-point of peak density of gametocytaemia in the CHMI-trans model.
5) To assess gametocyte infectiousness for Anopheles mosquitoes through mosquito feeding assay (Direct Skin Feeding Assay, DFA).

Study design

This study will be a single center, open label clinical trial. A total of 24

volunteers, in two cohorts (n=12), will be randomly assigned to two groups per cohort (n=6). Cohort A will be subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes (groups 1 and 2). Cohort B will be subjected to a standard blood stage challenge with ~2,800 Pf-infected erythrocytes by intravenous injection (groups 3 and 4) (see Figure 1, section 3).
Treatment is subsequently initiated to induce gametocytemia (treatment 1, T1) and to clear pathogenic asexual parasites whilst leaving gametocytes unaffected (treatment 2 and 3, T2 and T3). At the end of the study, treatment of all parasite stages is provided following national treatment guidelines (end treatment, ET).
Once malaria infections are detected by 18S qPCR positive at a density of 5,000 par/ml (sporozoite challenge) or on day 8 (blood stage challenge), all volunteers will be treated with a single oral subcurative low-dose of piperaquine (LD-PIP, 480 mg, T1). Daily blood samples will allow detailed quantification of gametocytes and gametocyte sex ratio. Using blood samples taken twice daily, the initial clearance of parasitemia will be carefully monitored. After T1, volunteers will receive a second treatment (T2, LD-PIP2, 480mg) if a recrudescence of asexual parasitemia (exceeding 1,500 par/ml by 18S qPCR) occurs before day 21 post challenge infection. On day 21 or when a recrudescence occurs after T2, volunteers in group 1 and 3 (LD-PIP/LD-PIP2/PIP) will be curatively treated with piperaquine (960mg) and group 2 and 4 (LD-PIP/LD-PIP2/SP) with sulfadoxine-pyrimethamine (1000mg/50mg). These treatment regimens cure asexual parasitemia while leaving immature and mature gametocytes unaffected(5). To ensure the radical clearance of all parasite stages, all volunteers will receive a final treatment (ET) according to national guidelines with atovaquone/proguanil (Malarone®) on day 36.

Intervention

All volunteers will be subjected to a standard controlled human malaria infection (CHMI) delivered by bites of five Pf-infected mosquitoes (3D7 clone) or a bloodstage malaria challenge (3D7 clone).

Study burden and risks

The study is associated with a period of intense clinical monitoring with daily site visits and bloodexaminations.The exact number of site visits and blood examinations per volunteers depends on the time to positive qPCR and potential recrudescence - with a maximum number of 45 study visits and a maximum of 500 mL collected blood. In addition 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

1. Subject is aged * 18 and * 35 years and in good health. ;2. Subject has adequate understanding of the procedures of the study and is able and willing (in the investigator*s opinion) to comply with all study requirements.;3. Subject is willing to complete an informed consent questionnaire and is able to answer all questions correctly. ;4. Subject is able to communicate well with the investigator and 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 (from day 4 (bloodstage challenge) 5 (sporozoite challenge) post-infection until T1+4 provided that the subject has had 2 consecutive negative 18S qPCR tests (at least 24 hours apart) following T1 treatment; or until day T3+3). ;5. The subject will remain within the Netherlands during the challenge period, will not travel to a malaria-endemic area during the study period, and is reachable (24/7) by mobile telephone throughout the entire study period. ;6. Subject agrees to their general practitioner being

informed and contacted about their participation in the study and agrees to sign a form to request the release by their General Practitioner (GP), and medical specialist when necessary, to the investigator(s), of any relevant medical information concerning possible contra-indications for participation in the study. ;7. The 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. ;8. For female subjects: subject agrees to use continuous adequate contraception** and not to breastfeed for the duration of study. ;9. Subject agrees to refrain from intensive physical exercise (disproportionate to the subjects usual daily activity or exercise routine) during the malaria challenge period.;10. Subject agrees to avoid additional triggers that may cause elevations in liver enzymes including alcohol from baseline up to 1 week post treatment. ;11. Subject has signed written informed consent to participate in the trial.

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 or >30 kg/m2 at screening. ;1.2. 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. ;1.3. A medical history of 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. Screening tests positive for Human Immunodeficiency Virus (HIV), active Hepatitis B Virus (HBV), Hepatitis C Virus (HCV) ;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. Any recent or current systemic therapy with an antibiotic or drug with potential anti-malarial activity (chloroquine, doxycycline, tetracycline, piperaquine, benzodiazepine, flunarizine, fluoxetine, tetracycline, azithromycin, clindamycin, erythromycin, hydroxychloroquine, etc.) (allowable timeframe for use at the Investigator*s discretion).;1.8. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years. ;1.9. Any history of treatment for severe psychiatric disease by a psychiatrist in the past year. ;1.10. History of drug or alcohol abuse interfering with normal social function in the period of one year prior to study onset, positive urine toxicology test for cocaine or amphetamines at screening or at inclusion, or positive urine toxicology test for cannabis at inclusion. ;2. For female subjects: positive urine pregnancy test at screening and/or at the baseline visit. ;3. Abnormal ALT/AST values on baseline ;4. Any history of malaria, positive serology for P. falciparum, or previous

participation in any malaria (vaccine) study. ;5. Known hypersensitivity to or contra-indications (including co-medication) for use of sulfadoxine-pyrimethamine, piperaquine, chloroquine, Malarone®, artemether-lumefantrine, primaquine or history of severe (allergic) reactions to mosquito bites. ;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 or the department of Internal Medicine. ;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

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	09-05-2018
Enrollment:	24
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	piperaquine
Generic name:	piperaquine
Product type:	Medicine
Brand name:	sulfadoxine-pyrimethamine
Generic name:	sulfadoxine-pyrimethamine

Ethics review

Approved WMO Date:	13-11-2017
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-02-2018
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
EudraCT	EUCTR2017-004005-40-NL
CCMO	NL63552.091.17
Other	will follow

Study results