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

Published: 14-04-2016
Last updated: 20-04-2024

Primary objectives:1) To evaluate the safety of four different CHMI-trans protocols in healthy malaria-naïve volunteers challenged with Plasmodium falciparum by sporozoite challenge. 2) To determine the best CHMI-trans protocol for induction of…

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

Summary

ID

NL-OMON44645

Source
ToetsingOnline

Brief title
CHMI-trans1

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: gametocytes, malaria, Plasmodium falciparum, transmission

Outcome measures

Primary outcome

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

- Prevalence of gametocytes in the CHMI-trans model in study groups.

Secondary outcome

- 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.

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 four different CHMI-trans protocols in healthy malaria-naïve volunteers challenged with Plasmodium falciparum by sporozoite challenge.
2) To determine the best CHMI-trans protocol for induction of stable gametocytaemia at densities detectable by qRT-PCR

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.

Study design

Single center, open label, randomized, sporozoite challenge study.
A total of 32 volunteers will be randomly assigned to four groups (n=8) and subjected to a standard controlled human malaria infection (CHMI) delivered by five Pf-infected mosquitoes (3D7 clone) (see Figure 1, section 3). Treatment is subsequently initiated to induce gametocytaemia (treatment 1, DT1) and to clear pathogenic asexual parasites whilst leaving gametocytes unaffected (treatment 2, DT2). 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 (day of treatment 1 [DT1]), groups 1 and 2 will be treated with a course of subcurative sulfadoxine-pyrimethamine (SP) (SP low, 500mg/25mg). Groups 3 and 4 will receive piperaquine (Pip) in a low-dose (Pip low, 480 mg). Daily blood samples will allow detailed quantification of gametocytes, gametocyte sex

ratio and ex vivo assessments of gametocyte fitness. Using blood samples taken twice daily, the initial clearance of parasitaemia will be carefully monitored. After DT1, volunteers will receive a curative treatment (DT2) when a recrudescence of asexual parasitaemia occurs or on day 21 post challenge infection, whichever comes first. Recrudescence of asexual parasitaemia will be carefully monitored until parasite densities reach 1,500 par/ml by 18S qPCR, at which time participants will receive the curative treatment (DT2). Volunteers in group 1 (SP low/SP high) will be treated with sulfadoxine-pyrimethamine (1000mg/50mg) and group 2 (SP low/Pip high) with piperaquine (960mg). Volunteers in group 3 (Pip low/Pip high) will be treated with piperaquine (960mg) and group 4 (Pip low/SP high) with sulfadoxine-pyrimethamine (1000mg/50mg). These treatment regimens for DT2 have been shown to cure asexual parasitaemia 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 42. In case a volunteer remains 18S qPCR and Pfs25 qRT-PCR negative for 7 days after DT1, final treatment with Malarone® will also be initiated and end of study will apply for the volunteer.

Intervention

All volunteers will be subjected to a standard controlled human malaria infection (CHMI) delivered by bites of five Pf-infected mosquitoes (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 50 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 5 post-infection until DT1+4 provided that the subject has had 2 consecutive negative 18S qPCR tests (at least 24 hours apart) following DT1 treatment; or until day DT2+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 has signed written informed consent to participate in the trial.;(*Acceptable forms of contraception include: established use of oral, injected or implanted hormonal contraceptives; intrauterine device or intrauterine system; barrier methods (condoms or diaphragm with additional spermicide); male partner*s sterilisation

(with appropriate post-vasectomy documentation of absence of sperm in the ejaculate); true abstinence when this is in line with the preferred and usual lifestyle of the subject; Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.)

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. 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 sulfadoxine-pyrimethamine, piperaquine, chloroquine, Malarone, artemether-lumefantrine, primaquine or history of severe (allergic) reactions to mosquito bites. ;5. Participation in any other clinical study in the 30 days prior to the start of the study or during the study period. ;6. Being an employee or student of the department of Medical Microbiology of the Radboudumc or the department of Internal Medicine. ;7. 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 phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-09-2016
Enrollment:	32
Type:	Actual

Medical products/devices used

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

Ethics review

Approved WMO Date:	14-04-2016
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	28-04-2016
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	EUCTR2016-001379-66-NL
CCMO	NL56659.091.16
Other	will follow