Coadministration of genetically attenuated Plasmodium falciparum *mei2 (GA2) sporozoites with adjuvants - a proof of principle study

Published: 31-08-2022
Last updated: 10-01-2025

This study has been transitioned to CTIS with ID 2024-516488-99-00 check the CTIS register for the current data. Primary objectives: 1. To assess the effect of experimental immunization with GA2 sporozoites by mosquito bite with and without co-...

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

Summary

ID

NL-OMON53441

Source
ToetsingOnline

Brief title
CoGA - Coadministration of GA2 sporozoites with adjuvants

Condition

- Protozoal infectious disorders

Synonym
Malaria

Research involving
Human

Sponsors and support

Primary sponsor: Leids Universitair Medisch Centrum

Source(s) of monetary or material Support: Vidi beurs van NWO,Letten Prize

Intervention

Keyword: falciparum, Malaria, Plasmodium, Vaccine

Outcome measures

Primary outcome

1. The time to parasitemia (qPCR >100p/mL) (prepatent period) after CHMI in participants immunized with the GA2 parasite with and without co-administration of an adjuvant compared to the infectivity controls.

2. Proportion of participants immunized with the GA2 parasite with and without co-administration of an adjuvant that do not develop parasitemia (qPCR >100p/mL) (sterile protection) after CHMI comparted the unadjuvanted group and the infectivity controls.

3. Frequency and magnitude of AEs in all study groups.

Secondary outcome

The composition and function of humoral and cellular immune responses following immunization with GA2 and adjuvants, and their association with protection against blood-stage malaria after CHMI.

Study description

Background summary

Despite initial successes, the efficacy of whole-sporozoite malaria vaccines in endemic areas is still limited. Immune hyporesponsiveness in endemic populations may be responsible for the somewhat disappointing results. Co-administration of adjuvants may improve the immunogenicity of whole-sporozoite vaccines. However, given the unconventional method of immunization, whereby the immunological effector mechanisms require antibody as

well as T cell responses occurring in the skin and in the liver induced by migrating whole parasites, it remains unclear if co-administered adjuvants will provide substantial advantage. Because animal models do not sufficiently replicate immune responses to live sporozoites in humans, this trial will be investigating the added value of co-administration of adjuvants with Plasmodium falciparum sporozoites by mosquito bites in a limited number of healthy volunteers. For this proof-of-concept study the Genetically Attenuated Parasite 2 (GA2 parasite) will be used, a modified Plasmodium falciparum strain that lacks the mei2 gene, causing it to arrest its development in the late liver-stage. GA2 thus enables full exposure to the liver stage antigens, whilst being safe to administer. The GA2 sporozoites will be co-administered with three products known to activate the immune response and are licensed for human use. Baccilus Calmette-Guérin (BCG) will target macrophages, a cell type which has also been shown to phagocytose sporozoites. Yellow fever vaccine strain 17D (YF-17D) is known for its activation of CD8+ T-cell responses potentially including the liver, an important effector organism. Imiquimod is a toll-like receptor ligand known to enhance responses of skin-administered vaccines. We will investigate whether adding these adjuvants to the GA2 sporozoites may increase their immunogenicity.

Study objective

This study has been transitioned to CTIS with ID 2024-516488-99-00 check the CTIS register for the current data.

Primary objectives:
1. To assess the effect of experimental immunization with GA2 sporozoites by mosquito bite with and without co-administration of different adjuvants on the pre-patent period after controlled human malaria infection (CHMI).
2. To assess the proportion of participants that acquire sterile protection against CHMI after single immunization with GA2 sporozoites with and without co-administration with different adjuvants.
3. To analyze the safety and tolerability of co-administration of GA2 sporozoites with different adjuvants.

Secondary objectives:
1. To compare immune responses after co-administration of GA2 sporozoites with different adjuvants.

Study design

This study will be an adaptive single center, randomized controlled clinical proof-of-principle trial of GA2 parasites co-administered with adjuvants in 65 healthy, BCG-, YF-17D-, and malaria-naïve male and female participants. There will be three to four stages in the trial. In stage A, a single immunization with 50 GA2-infected mosquito bites without co-administration of

adjuvants will be assessed. This stage will consist of two groups:
- Ten participants will receive unadjuvanted immunization with GA2-infected mosquitoes.
- Five participants (infectivity controls) will be mock immunized with uninfected mosquitoes.
To assess the added value of adjuvants on the immunizing effects of a single GA2 immunization, a protective efficacy <=70% must be found in stage A to progress in stage B. If in stage A the protective efficacy after a single GA2 immunization with 50 mosquito bites is >70%, then we will first progress to stage A2 with a lower *dose* of GA2 immunization by 10 mosquito bites.
In stage A2, a single immunization with 10 GA2 infected mosquito bites without co-administration of adjuvants will be assessed. This stage will consist of three groups:
- Ten participants will receive unadjuvanted immunization with 10 GA2-infected mosquitoes.
- Five participants will receive unadjuvanted immunization with 50 GA2 infected mosquitoes. In this group skin biopsies will be done as well to assess innate skin responses which may orchestrate the findings of high protective efficacy found in stage A. To have a negative control skin biopsy to compare with, the participants in this group will also be bitten by 50 uninfected mosquitoes in the other arm. Skin biopsies of both arms will be taken two days post-immunization. Participants need to give their consent if they do or do not want to participate in the skin biopsy group. So this group is not randomized.
- Five participants (infectivity controls) will be mock immunized with 10 uninfected mosquitoes.

Results from stage A and optional stage A2 will be reviewed by the safety monitoring committee (SMC). Continuation to stage B will be discussed and criteria to transition and continue from stage B to C will be designed in accordance with SMC and submitted to the CCMO. If in stage A2 the protective efficacy of a single immunization with 10 GA2 infected mosquito bites is again >70% then there will be no progression to stage B and the study will be stopped.

In stage B of the trial, the co-administration with the three adjuvants will be assessed. This stage will consist of four groups:
• Five participants will receive immunization with GA2-infected mosquitoes co-administered with a BCG-vaccination.
• Five participants will receive immunization with GA2-infected mosquitoes co-administered with an intradermal YF-17D vaccination.
• Five participants will receive immunization with GA2-infected mosquitoes co-administered imiquimod cream.
• Two infectivity controls will be mock immunized with uninfected mosquitoes.

Based on results of stage B, the most favorable adjuvant can be selected for further assessment in stage C in consultation with the SMC.
The choice of the adjuvant and whether it is useful to continue with stage C

will be made by the PI after consulting the safety monitoring committee (SMC), and will be based on results on tolerability, time to patency and immunology. Criteria for continuation with stage C will be based on findings in stage B and will be determined before starting stage C. Stage C will consist of three groups:
• Five additional participants will receive immunization with GA2-infected mosquitoes co-administered with the adjuvant.
• Five participants will receive unadjuvanted immunization with GA2-infected mosquitoes.
• Three infectivity controls will be mock immunized with uninfected mosquitoes.

Due to different methods of administration (injection for BCG/YF-17D and topical application for imiquimod) and due to specific side-effects (e.g. BCG-ulcer after BCG vaccination), adjuvanted groups and the skin biopsy group will not be blinded. Unadjuvanted groups and infectivity controls, however, will be blinded to both participants and clinical study staff.

After immunization, participants will have visits for collection of immunology samples, safety labs and adverse events (AEs) on day 2, 6, 9 and 14 after immunization. Six weeks after the immunization, all immunized participants and infectivity controls will undergo CHMI trough the bites of 5 mosquitos infected with wild-type Plasmodium falciparum 3D7 sporozoites.
On day 6 until day 21 and on day 28 after infection, participants will be followed on an out-patient basis to determine AEs and parasite loads detected by qPCR. As soon as blood stage parasitemia is detected (cut-off >100p/mL) or at the latest 28 days after CHMI participants will be treated with a curative regimen of antimalarials (atovaquone/proguanil or alternatively artemether/lumefantrine) dosed to local hospital guidelines. End of follow-up will be 6 months after CHMI.

Intervention

Immunization with the bites of 10 or 50 GA2 infected mosquitos with and without co-administration of an adjuvant (BCG, YF-17D or imiquimod), followed by a CHMI after 42 days.

Study burden and risks

Risks for participants in the studie are related to:
• Potential breakthrough blood-stage infection after exposure to the GA2 parasite (risk deemed very low since no breakthrough blood-stage infections occurred in previous GA2 trial);
• Systemic adverse events related to exposure to the GA2 parasite and/or the BCG, YF-17D vaccination and imiquimod;
• Local adverse events related to BCG- YF-17D-vaccination, skin biopsy, mosquito bites or imiquimod;

• Potential blood-stage infection after CHMI;
• Side effects of antimalarial treatment.
Burden: participants will be exposed to the bites of mosquitoes infected with GA2 parasites. After the exposure to the GA2, there will be four out-patient visits.
Subsequently, participant will undergo CHMI and there will be a 28-day-period of close monitoring with frequent ambulatory visits and blood examinations. In addition, physical examinations will be performed when clinically indicated and participants will be asked to complete a diary of adverse events on a daily basis. When testing positive for malaria, volunteers will be treated with antimalarials After this period, all participants not yet treated with antimalarials will have to take antimalarial treatment (when not already treatment in case of parasitemia after CHMI).
Participants will have to visit the trial center on approximately 30 occasions, the maximum cumulative amount of blood collected per 4 months will be 500 mL for each participant.
Group relatedness: in the immunization phase, participant burden is expected to be equal among all groups apart from known side effects to BCG, YF-17D, imiquimod and skin biopsies. After CHMI, all infectivity controls are expected to develop malaria. In other groups, an unknown fraction of the group may not develop malaria.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Inclusion criteria

In order to be eligible to participate in this study, a participant must meet all of the following criteria:
1. Participant is aged >=18 and <=35 years and in good health.
2. Participant has adequate understanding of the procedures of the study and agrees to abide strictly thereby.
3. Participant is able to communicate well with the investigator
4. Participant is available to attend all essential study visits.
5. Participant agrees that his/her general practitioner (GP) will be informed about participation in the study.
6. Participant agrees to refrain from blood donation to Sanquin or for other purposes throughout the study period and for a defined period thereafter according to Sanquin guidelines.
7. Participants of child bearing potential (i.e., have an uterus and are neither surgically sterilized nor post-menopausal) agree to use adequate contraception and to not breastfeed for the duration of study.
8. Participant agrees to refrain from intensive physical exercise (disproportionate to the participants* usual daily activity or exercise routine) for twenty-one days following the immunization and during the malaria challenge period.
9. Participant signs informed consent.

Exclusion criteria

1. Any history, or evidence at screening, of clinically significant symptoms, physical signs or abnormal laboratory values suggestive of systemic conditions which could compromise the health of the participant during the study or interfere with the interpretation of the study results. These include, but are not limited to, any of the following: a. Body Mass Index (BMI) >35.0 kg/m2 at screening. b. An elevated risk of cardiovascular disease, defined as: i. An estimated ten-year risk of fatal cardiovascular disease of >=5% at screening, as determined by the Systematic Coronary Risk Evaluation 2 (SCORE2) . See Appendix 1 for the SCORE2 risk classification; ii. History, or evidence at screening, of clinically significant arrhythmia*s, prolonged QT-interval or other clinically relevant ECG abnormalities; or iii. A positive family history of cardiac events in first- or second-degree relatives (according to the system used in medical genetics) <50 years old. c. Known functional asplenia, sickle cell

trait/disease, thalassemia trait/disease or G6PD deficiency. d. History of epilepsy in the period of five years prior to study onset, even if no longer on medication. e. Positive HIV, HBV or HCV screening tests. f. Chronic use of i) immunosuppressive drugs, ii) antibiotics, iii) or other drugs that might have an influence on the immune system (excluding inhaled and topical corticosteroids and incidental use of oral anti-histamines), within three months prior to study onset or expected use of such during the study period. g. Skin disease affecting the site of administration in such a way that administration of mosquito bites or adjuvants is deemed impossible by investigator. h. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past five years. i. Any history of treatment for severe psychiatric disease by a psychiatrist in the past year. j. History of drug or alcohol abuse interfering with normal social functioning in the period of one year prior to study onset, positive urine toxicology test for cocaine or amphetamines at screening. 2. For participants of child bearing potential: breastfeeding, or positive urine pregnancy test prior to immunization or prior to CHMI. 3. Any history of malaria or previous participation in any malaria (vaccine) study or CHMI. 4. Known hypersensitivity to or contra-indications for both atovaquone/proguanil or artemether/lumefantrine. QT prolonging drugs are only considered an exclusion criterion when QT prolongation is observed at the ECG at screening. 5. A history of severe (allergic) reactions to mosquito bites. 6. Any history of infection with mycobacteria or BCG vaccination (only in stage B and C). 7. Any history of infection with yellow fever virus or yellow fever vaccination (only in stage B and C). 8. Planned vaccination two weeks before immunization. When necessary due to medical reasons, exceptions can be made in accordance with the PI. 9. For participants in skin biopsy group: increased risk of complications after skin biopsy (e.g.use of anticoagulants, immunosuppressive medication or having tattoo's on the biopsy region) 10. Participation in any other clinical study assessing an investigational medical product in the 30 days prior to the start of the study or during the study period. 11. Any condition or situation that could influence the independent consent of participant (e.g. being a direct colleague or family member of study personnel. 12. Any other condition or situation that would, in the opinion of the investigator, place the participant at an unacceptable risk of injury or render the participant unable to meet the requirements of the protocol or would compromise the integrity of the data.

Study design

Design

Study type:	Interventional

Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Prevention

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-02-2023
Enrollment:	65
Type:	Actual

Medical products/devices used

Product type:	Medicine
Generic name:	Genetic modified organism
Product type:	Medicine
Brand name:	Aldara 5% cream
Generic name:	Imiquimod 5% cream
Registration:	Yes - NL outside intended use
Product type:	Medicine
Brand name:	BCG vaccine AJV
Product type:	Medicine
Brand name:	GA2 parasite
Product type:	Medicine
Brand name:	Stamaril

Ethics review

Approved WMO

Date:	31-08-2022
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)

Approved WMO

Date:	30-01-2023
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-12-2023
Application type:	Amendment
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	22-03-2024
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
EU-CTR	CTIS2024-516488-99-00
EudraCT	EUCTR2022-002646-40-NL
ClinicalTrials.gov	NCT05468606
CCMO	NL82130.000.22