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Investigating resistance to DHA-PIP for the treatment of Plasmodium falciparum malaria and chloroquine for the treatment of Plasmodium vivax malaria in Yunnan, China

Submission date
13/04/2020

Recruitment status
No longer recruiting

Registration date
17/04/2020

Overall study status
Completed

Last Edited
13/11/2023

Condition category
Infections and Infestations

[_] Prospectively registered
[_] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
Malaria is caused by infection of blood cells with Plasmodium parasites. People with malaria feel unwell and typically have fever, tiredness, vomiting, and headaches. Malaria can lead to death, and if not treated, it can cause repeated bouts of illness. The World Health Organization (WHO) recommends artemisinin-based combination therapy (ACT) for the initial treatment of malaria with no complications caused by Plasmodium falciparum. Chloroquine is recommended for treatment of Plasmodium vivax malaria. However, there have been reports of resistance of the parasite infection to treatment with these drugs in countries such as Myanmar, Thailand, Vietnam and Cambodia that border China. This study aims to investigate how effective these malaria treatments are in Yunnan, a province of China in the south-east of the country that borders Myanmar, Laos and Vietnam.

Who can participate?
People aged 6 months to 60 years who have malaria and are infected with Plasmodium falciparum or Plasmodium vivax, but not both.

What does the study involve?
People will receive the usual treatment for each type of parasite in the health centre for 3 days. Those with Plasmodium falciparum infection will receive DHA-PIP (dihydroartemisinin and piperaquine) and will be followed up for 42 days. Those with Plasmodium vivax infection will receive chloroquine and will be followed up for 28 days. The follow-up will include blood tests to investigate whether the parasite has been fully cleared from the blood.

What are the possible benefits and risks of participating?
The medicines may have some minor side effects. It is also possible that they may cause some problems that are unexpected; however, the researchers and healthcare staff will follow the participants closely and keep track of these effects, if they arise, and of any other problems. Participants will be given a telephone number to call if they notice anything out of the ordinary

or if they have concerns or questions. They can also come to the health facility at any time and ask to see the doctor or to speak with a doctor on the telephone. If they experience side-effects, the researchers may use some other medicine, free of charge, to help to reduce the symptoms or reactions, or they may stop one or more of the medicines. If this is necessary, it will be discussed together with participants. Participants will always be consulted before any changes are made to the treatment.

Where is the study run from?
The National Institute of Parasitic Disease (China)

When is the study starting and how long is it expected to run for?
June 2012 to December 2016

Who is funding the study?
The WHO, the National Natural Science Foundation of China and the Global Fund to Fight AIDS, Tuberculosis and Malaria

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
Nil known

Study information

Scientific Title
Efficacy and safety of DHA-PIP for the treatment of uncomplicated Plasmodium falciparum malaria and chloroquine for the treatment of Plasmodium vivax malaria in Yunnan, China

Study objectives
Based on the fact that "suspected resistance" and "confirmed resistance" of falciparum malaria to ACT arose and spread in South-east Asian locations, such as Myanmar, Thailand, Viet Nam and Cambodia, it is important to continuously monitor the efficacy of DHA-PIP in these sites and neighbouring areas and to monitor its distribution or spread in Yunnan. Additionally, more studies are needed to confirm the relationship of some K13 mutations with anti-malaria drug resistance.

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 19/06/2012, WHO Office for the Western Pacific Ethics Review Committee (no address, telephone number or email), ref: 2012.11.CHN.04.MVP
2. Approved 06/09/2013, Chinese Center for Disease Control and Prevention Ethical Review

Committee (155 Changbai Road, Changping District, Beijing, China 102206; +86-10-58900001; chenchunming@chinacdc.cn), no reference number
3. Approved 21/03/2016, National Institute of Parasitic Diseases Ethical Review Committee (207 Ruijin Er Road, Shanghai, China 200025; +86 21 64377008; lizhen@nipd.chinacdc.cn), no reference number

Study design
Observational surveillance study

Primary study design
Observational

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Uncomplicated Plasmodium falciparum and vivax malaria

Interventions
This surveillance study is a one-arm prospective evaluation of clinical and parasitological responses to directly observed treatment for uncomplicated malaria. People with uncomplicated falciparum and vivax malaria who meet the study inclusion criteria will be enrolled, treated on-site with 3-day DHA-PIP (dihydroartemisinin + piperaquine) and chloroquine, and monitored for 42 and 28 days, respectively. The follow-up will consist of a fixed schedule of check-up visits and corresponding clinical and laboratory examinations. On the basis of the results of these assessments, the patients will be classified as having therapeutic failure (early or late) or an adequate response. The proportion of patients experiencing therapeutic failure during the follow-up period will be used to estimate the efficacy of the study drug(s). PCR analysis will be used to distinguish between a true recrudescence due to treatment failure and episodes of re-infection.

Treatment(s) and follow-up: Patients infected with P. falciparum will be treated with DHA-PIP at a dose of 2 mg/kg/day DHA and 16 mg/kg/day PIP for 3 days. Patients with P. vivax infection will be treated with chloroquine at a total dose of 25 mg base/kg body weight over 3 days. Clinical and parasitological parameters will be monitored over a 42- or 28-day follow-up period to evaluate drug efficacy.

Intervention Type
Drug

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Dihydroartemisinin + piperaquine, chloroquine

Primary outcome(s)
1. Early treatment failure, defined as any one of the following:
1.1. Danger signs or severe malaria on day 1, 2 or 3 in the presence of parasitaemia
1.2. Parasitaemia on day 2 higher than on day 0, irrespective of axillary temperature
1.3. Parasitaemia on day 3 with axillary temperature ≥37.5°C

1.4. Parasitaemia on day 3 ≥25% of count on day 0
2. Late clinical failure, defined as any one of the following:
2.1. Danger signs or severe malaria in the presence of parasitaemia on any day between day 4 and day 28 for P. vivax patients and day 42 for P. falciparum patients in patients who did not previously meet any of the criteria of early treatment failure
2.2. Presence of parasitaemia on any day between day 4 and day 28 for P. vivax patients and day 42 for P. falciparum patients with axillary temperature ≥37.5°C (or history of fever) in patients who did not previously meet any of the criteria of early treatment failure
3. Late parasitological failure, defined as presence of parasitaemia on any day between day 7 and day 28 for P. vivax patients and day 42 for P. falciparum patients with axillary temperature <37.5°C in patients who did not previously meet any of the criteria of early treatment failure or late clinical failure
4. Adequate clinical and parasitological response, defined as absence of parasitaemia on day 28 for P. vivax patients and day 42 for P. falciparum patients, irrespective of axillary temperature, in patients who did not previously meet any of the criteria of early treatment failure, late clinical failure or late parasitological failure

Recrudescence will be distinguished from re-infection by polymerase chain reaction (PCR) analysis.

Key secondary outcome(s))
The frequency and nature of adverse events

Completion date
28/02/2017

Eligibility

Key inclusion criteria
1. Age between 6 months and 60 years
2. Mono-infection with P. falciparum or P. vivax detected by microscopy
3. Mono-infection with P. falciparum detected by microscopy with parasitaemia of 500-100,000 /µl asexual forms
4. Mono-infection with P. vivax detected by microscopy with parasitaemia of ≥250/µl asexual forms
5. Axillary or tympanic temperature ≥37.5°C or oral or rectal temperature of ≥38°C or history of fever during the past 24 h
6. Able to swallow oral medication
7. Able and willing to comply with the study protocol for the duration of the study and to comply with the study visit schedule
8. Informed consent from the patient or from a parent or guardian in the case of children aged less than 18 years
9. Informed assent from any minor participant aged from 12 to age of 18 years
10. Consent for pregnancy testing from female of child-bearing potential and from their parent or guardian if under the age of 18 years

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
6 months

Upper age limit
60 years

Sex
All

Key exclusion criteria
1. Presence of general danger signs in children aged under 5 years or signs of severe falciparum malaria according to WHO definitions
2. Weight under 5 kg
3. Mixed infection or mono-infection with another Plasmodium species detected by microscopy
4. Presence of severe malnutrition defined as a child aged 6-60 months whose weight-for-height is below –3 z-score, has symmetrical oedema involving at least the feet or has a mid-upper arm circumference < 115 mm)
5. Presence of febrile conditions due to diseases other than malaria (e.g. measles, acute lower respiratory tract infection, severe diarrhea with dehydration) or other known underlying chronic or severe diseases (e.g. cardiac, renal and hepatic diseases, HIV/AIDS)
6. Regular medication, which may interfere with antimalarial pharmacokinetics
7. History of hypersensitivity reactions or contraindications to any of the medicine(s) being tested or used as alternative treatment(s)
8. Positive pregnancy test or breastfeeding
9. Unable to or unwilling to take pregnancy test or to use contraception for women of child-bearing age and who are sexually active

Date of first enrolment
23/04/2012

Date of final enrolment
28/12/2016

Locations

Countries of recruitment
China

Study participating centre
National Institute of Parasitic Diseases, China CDC
No.207, Ruijin Er Road
Shanghai
China
200025

Study participating centre
Yunnan Provincial Institute of Parasitic Diseases
No. 6 West Yuan Road
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Sponsor information

Organisation
World Health Organization Regional Office for South-East Asia

ROR
https://ror.org/02wae9s43

Organisation
National Natural Science Foundation of China

Funder(s)

Funder type
Other

Funder Name
World Health Organization

Alternative Name(s)
, , Всемирная организация здравоохранения, Organisation mondiale de la Santé, Organización Mundial de la Salud, WHO, , ВОЗ, OMS

Funding Body Type
Government organisation

Funding Body Subtype
International organizations

Location
Switzerland

Funder Name
National Natural Science Foundation of China

Alternative Name(s)
Chinese National Science Foundation, Natural Science Foundation of China, National Science Foundation of China, NNSF of China, NSF of China, National Nature Science Foundation of China, Guójiā Zìrán Kēxué Jījīn Wěiyuánhuì, , NSFC, NNSF, NNSFC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
China

Funder Name
Global Fund to Fight AIDS, Tuberculosis and Malaria

Alternative Name(s)
Global Fund, The Global Fund, The Global Fund to Fight AIDS, Tuberculosis and Malaria, Fonds mondial de lutte contre le sida, la tuberculose et le paludisme, Fonds mondial, Le Fonds mondial, Globalen Fonds, Der Globalen Fonds, GFATM

Funding Body Type
Private sector organisation

Funding Body Subtype
International organizations

Location
Switzerland

Results and Publications

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output	Date	Date	Peer	Patient-

type	Details	created	added	reviewed?	facing?
Other publications	Genetic analysis of P. falciparum parasites collected from 2012 to 2016 along the China-Myanmar border	10/11/2023	13/11/2023	Yes	No