ISRCTN35227717 https://doi.org/10.1186/ISRCTN35227717

Oseltamivir for treatment of thrombocytopenia and plasma leakage in dengue

Submission date	Recruitment status	[X] Prospectively registered
08/01/2018	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
12/01/2018	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
10/01/2022	Infections and Infestations	

Plain English summary of protocol

Background and study aims
Dengue is a virus caused by mosquitos. Symptoms include high fever, heaches, vomiting, muscle pains and skin rashes. Low platelets counts (thrombocytopenia) are very common in dengue. Having a low blood platelet count means that the body cannot form blood clots to stop bleeding. Increasing evidence suggests that low platelet numbers play a role in plasma leakage and the bleeding complications of dengue. Patients with dengue can remove certain acids causing a lower amount of platelets. This can be reversed by the neuraminidase inhibitor called oseltamivir. This medication is an approved drug for treatment of influenza. It is speculated that oseltamivir may fasten platelet recovery in dengue-induced thrombocytopenia and prevent plasma leakage. The aim of this study is to investigate whether oseltamivir reduces the time needed for platelet numbers to recover and/or prevent plasma leakage in patients with acute dengue with moderate to severe thrombocytopenia.

Who can participate?
Adults aged 16 and older who go to the hospital for dengue.

What does the study involve?
Participants are randomly allocated to one of two groups. Those in the first group continue with their standard level of care. Those in the second group receive oseltamiriv phosphate twice a day taken by mouth for a maximum of 5 days or when their platelet number reaches a certain level. Platelet numbers are determined twice a day using an ultrasound (using sound waves to create images) and blood tests. Participants are followed three weeks after the start of the study to assess if there are any complications.

What are the possible benefits and risks of participating?
Participation in this study is associated with possible risks and benefits. Possible benefits for participants are that daily laboratory tests are covered by the study and that daily ultrasonography for plasma leakage will be performed. In case the hypothesis that oseltamivir promotes recovery of dengue-associated thrombocytopenia is true, participants randomized to the oseltamivir may be discharged from hospital earlier. There is extensive clinical experience with oseltamivir and severe side effects are uncommon. Nonetheless, the current study employs oseltamivir for a new, unregistered indication and side effects cannot be excluded.

Where is the study run from?
1. RS Nasional Diponegoro (Indonesia)
2. RSUD K.R.M.T. Wongsonegoro (Indonesia)
3. William Booth Hospital (Indonesia)
4. RSUD Kartini (Indonesia)
5. RSAU Salamun (Indonesia)
6. RSUP Dr. Hasan Sadikin (Indonesia)
7. RSUD Al-Ihsan (Indonesia)

When is the study starting and how long is it expected to run for?
September 2017 to December 2019

Who is funding the study?
ZonMw (Netherlands)

Who is the main contact?
1. Dr Rahageng Tunjunputri (Public)
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Contact information

Type(s)
Public

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Additional identifiers

Protocol serial number
650/EC/FK-RSDK/XI/2017

Study information

Scientific Title
Treatment Of Thrombocytopenia with Oseltamivir in acute dengue virus infection (TOTO-trial): a randomized, placebo controlled, multicenter trial

Acronym
TOTO

Study objectives
1. Oseltamivir phosphate given to patients with thrombocytopenia in acute dengue reduces the time to platelet recovery (platelets >100 x 10^12/L)
2. Oseltamivir phosphate given to patients with thrombocytopenia in dengue reduces the incidence of dengue-associated plasma leakage

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee of the Faculty of Medicine Diponegoro University and Dr Kariadi Hospital, 27 /12/2017, ref: 650/EC/FK-RSDK/XI/2017

Primary study design
Interventional

Study design
Phase 2 multicentre randomized placebo-controlled double-blinded interventional trial

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Dengue

Interventions
The study is designed as a phase 2, multicentre, randomized, placebo-controlled, double-blinded intervention trial.
Participants will be randomized using block randomization in a 1:1 allocation ratio.

The trial is double-blinded, i.e. both researchers/study personnel, physicians and participants are blinded.

The intervention tested is oseltamivir phosphate 75 mg BID orally (intervention group) or placebo (control group) until platelet number reaches >100 x 10(9)/L or for a maximum of 5 days. Patients are randomised using block randomization with variable block size.

Platelet numbers are determined 2 times/daily in all participants and plasma leakage are assessed daily using ultrasonography and by twice daily haematocrit.

Participants will be followed up daily until discharge from hospital or until their platelet count has reached ≥ 100 x 109/l. A follow-up visit at home will be performed three weeks after randomization to assess for late complications and to obtain convalescence laboratory measurements.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Oseltamivir phosphate

Primary outcome(s)
Current primary outcome measures as of 25/02/2019:
1. Time to platelet recovery (platelet count ≥ 100 x 109/l) is measured using twice daily platelet count measurement from enrollment until discharge or until platelet count ≥ 100 x 109/l
2. Plasma leakage is measured by twice daily haematocrit, daily ultrasonography (looking for gall bladder wall thickness, ascites and pleural fluid) and plasma markers (e.g. Syndecan-1) from enrollment until discharge or until platelet count ≥ 100 x 109/l

Previous primary outcome measures:
1. Time to platelet recovery (platelet count ≥ 100 x 109/l) is measured using twice daily platelet count measurement from enrollment until discharge or until platelet count ≥ 100 x 109/l
2. Plasma leakage is measured by twice daily haematocrit and daily ultrasonography (looking for gall bladder wall thickness, ascites and pleural fluid) from enrollment until discharge or until platelet count ≥ 100 x 109/l

Key secondary outcome(s)
Current secondary outcome measures as of 25/02/2019:
1. Safety of oseltamivir use in dengue is measured using daily measurement of creatinine and liver enzymes from enrollment until discharge or until platelet count ≥100 x 109/l for a maximum of five days and at week 3 post-enrollment
2. Rate of change of platelet count is measured twice daily using platelet count measurement at 24, 48 and 5 days
3. Number of participants developing severe thrombocytopenia measured using platelet count measurement at enrollment until discharge or until platelet count ≥ 100 x 109/l.
4. Dengue-related complications, especially clinical bleeding is assessed daily using WHO

bleeding scores at enrollment until discharge or until platelet count ≥ 100 x 109/l
5. Markers of inflammation, coagulation and endothelial perturbation is measured using daily plasma samples

Previous secondary outcome measures:
1. Safety of oseltamivir use in dengue is measured using daily measurement of creatinine and liver enzymes from enrollment until discharge or until platelet count ≥100 x 109/l for a maximum of five days and at week 3 post-enrollment
2. Rate of change of platelet count is measured twice daily using platelet count measurement at 24, 48 and 5 days
3. Number of participants developing severe thrombocytopenia measured using platelet count measurement at enrollment until discharge or until platelet count ≥ 100 x 109/l.
4. Dengue-related complications, especially clinical bleeding is assessed daily using WHO bleeding scores at enrollment until discharge or until platelet count ≥ 100 x 109/l
5. Flow cytometric platelet studies, including platelet activation and reactivity assays as well as platelet sialic acid expression is measured daily using antibodies against P-selectin and the binding of fibrinogen to platelets in unstimulated samples and after stimulation with platelet agonists. Platelet sialic acid content is measured using the lectins SNA, MAL-II and RCA.
6. Markers of inflammation, coagulation and endothelial perturbation is measured using daily plasma samples

Completion date
31/12/2019

Eligibility

Key inclusion criteria
1. Admission to hospital
2. Aged 18 years and above; Updated 01/11/2018: Aged 16 years and above
3. Positive result of NS1 rapid test (proven dengue) or positive for acute dengue serology with probable dengue criteria as defined in WHO 2009 criteria
4. Fever <=6 days
5. Platelet count <70 x 10^9/L

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Total final enrolment

70

Key exclusion criteria
1. Symptoms or signs of another infectious disease
2. Pregnancy or breastfeeding
3. Persistent or recurrent clinical bleeding such as epistaxis, haematemesis, haematochezia, melena, intermenstrual bleeding
4. Chronic liver or kidney disease or active haematological disease
5. Estimated creatinine clearance at moment of enrolment <70 ml/min
6. ALT value > 3x the upper limit of normal
7. Use of platelet function inhibitors or anticoagulants
8. Platelet transfusion during the current hospitalization
9. In patients with earlier platelet count available in past days: platelet number already recovering

Date of first enrolment
13/01/2018

Date of final enrolment
31/07/2019

Locations

Countries of recruitment
Indonesia

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Sponsor information

Organisation
Center for Tropical and Infectious Diseases (Centrid)

Funder(s)

Funder type
Charity

Funder Name
ZonMw

Alternative Name(s)
Netherlands Organisation for Health Research and Development

Funding Body Type
Private sector organisation

Funding Body Subtype
Other non-profit organizations

Location
Netherlands

Results and Publications

Individual participant data (IPD) sharing plan
After publication of the trial results, data will be stored in DANS repository (https://dans.knaw.nl). The type of data stored are quantitative data, including allocation to treatment arm, demographics of the study participants (age, sex), platelet data (counts, activation and reactivity, sialic acid content), data on plasma leakage and safety data (renal and liver function). Data will be available on request (restricted access). Data will be stored anonymized. Participants have given consent for anonymized data to be stored in a repository.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		07/01/2022	10/01/2022	Yes	No