CompLement C5 Antibodies for decreasing brain injury after aneurysmal Subarachnoid Hemorrhage: safety and proof-of-concept

Published: 10-01-2018
Last updated: 04-01-2025

This study aims to investigate the biological efficacy and safety of eculizumab in patients with aneurysmal SAH.

Ethical review	Approved WMO
Status	Completed
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON48636

Source
ToetsingOnline

Brief title
CLASH

Condition

- Central nervous system vascular disorders
- Aneurysms and artery dissections

Synonym
Hemorrhagic stroke, Stroke

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht

Source(s) of monetary or material Support: ZonMW ,"Alexion Pharmaceuticals",Alexion Pharmaceuticals

Intervention

Keyword: Delayed cerebral ischemia, Early brain injury, Eculizumab, Subarachnoid hemorrhage

Outcome measures

Primary outcome

The primary outcome measure is biological effectivity determined by the

concentration of C5a in CSF.

Secondary outcome

The secondary outcome measures are the occurrence of adverse events (AEs) and

serious adverse events (SAEs), plasma and CSF parameters of inflammation,

quality of life (QoL), functional, and cognitive outcomes, and the presence and

volume of cerebral infarction.

Study description

Background summary

Important determinants of poor functional outcome after aneurysmal SAH are early brain injury (brain injury <72 hours after ictus) and delayed cerebral ischemia (4-14 days after the bleeding). No treatment exists to reduce early brain injury and the effects of current strategies (nimodipine, euvolemia) to prevent delayed cerebral ischemia are only modest. The inflammatory response is considered to play a key role in the pathogenesis of early brain injury and delayed cerebral ischemia after aneurysmal SAH. Previous studies found that the complement cascade is activated in patients with SAH and associated with poor functional outcome. Recent research shows that brains of patients who died from aneurysmal SAH had much higher complement expression than brains from controls. In a mouse model of SAH, treatment of mice with C5 antibodies resulted in a decrease in brain injury compared to mice without treatment. We hypothesize that treatment with C5 antibodies decreases early brain injury and delayed cerebral ischemia in patients with aneurysmal SAH and thereby improves clinical

condition. In the current trial, we will investigate the biological effect and safety of eculizumab (C5 antibodies) in patients with aneurysmal SAH.

Study objective

This study aims to investigate the biological efficacy and safety of eculizumab in patients with aneurysmal SAH.

Study design

This will be a randomized, open-label phase II clinical trial with blinded outcome assessment. Patients admitted to the hospital within <=11.5 hours after ictus and patients with a confirmed aneurysmal subarachnoid hemorrhage are eligible for this study. Informed consent will be obtained from the patient or a legally acceptable surrogate (if the patient is incapacitated). In case the patient was incapacitated at admission, the patient will be asked for informed consent as soon as the patient can give informed consent. This will be checked daily by the treating physician or investigator. If the patient or a legally accepted surrogate gives informed consent, randomization starts. The outcome of the randomization will either be 'eculizumab treatment and care as usual' or only 'care as usual'. Depending on the outcome, eculizumab will be administered (as soon as possible but not later than 12 hours after ictus) in addition to the standard care or only standard care will be given.

Intervention

The intervention group will receive intravenous eculizumab infusions. The control group will receive standard treatment for SAH (no placebo).

Study burden and risks

Risks associated with eculizumab:
Eculizumab has been approved for treatment of patients with Paroxysmal Nocturnal Hemoglobinuria (PNH) and Atypical Hemolytic Uremic Syndrome (aHUS). The most common AE reported during treatment with eculizumab is headache (occurred mostly in the initial phase). Patients who are treated with eculizumab show an increased susceptibility to infections, especially to infections with the meningococcus bacteria. To address the increased risk of meningococcal infection, patients in the intervention group will receive prophylactic treatment with ciprofloxacin during the first four weeks after ictus. In addition, throat- and rectal swaps will be performed weekly in all patients in the intervention group to test for carriership/colonization (yeast) and to determine drug-resistance (multi-drug resistance bacteria and yeast). Patients in the intervention group with a central line/drain and a positive swap will receive antifungal prophylaxis next to the antibiotic prophylaxis. If drug resistance occurs, prophylactic therapy will be adjusted in consultation

with the microbiologist. Before discharge, patients in the intervention group will receive safety instructions and a patient safety card. These patients will be asked to carry the patient safety card on their person until three months after the last administration of the study drug. The control group will not receive antibiotics or antifungal therapy.

Risks associated with study procedures:
Complications of CSF withdrawal from an external ventricular or lumbar drain include a possible increased risk of infection. If CSF withdrawal from a drain is not possible, a lumbar puncture will be performed. Potential risks consist of a lumbar puncture are: 1) post-lumbar puncture headache; 2) back pain and; 3) radicular pain or numbness. Very rare complications of a lumbar puncture include: 1) infection; 2) bleeding; and 3) abducens palsy. Withdrawal of blood poses very minor risks including bruising, pain, swelling and redness, possible infection at the injection site, and a rare risk of fainting. There is no increased risk for any of the other examinations performed (e.g. daily neurological examination, throat- and rectal swaps, magnetic resonance imaging (MRI) without gadolinium, cognitive-, QoL, and modified Ranking scale testing).

Risks associated with antibiotic use (only for the intervention group) and if necessary antifungal prophylaxis (only in the intervention group in patients with a central line/drain and a positive swap)
A potential risk of antibiotic/antifungal therapy is resistance. With throat- and rectal swaps, we will closely monitor drug resistance. In case a patient develops drug resistance, the microbiologist will be consulted to discuss other options for prophylaxis. We exclude patients with a high risk of drug resistant bacteria or yeast. Potential side-effects of antibiotic use are described in C1 ' Onderzoeksprotocol' and the E1/E2 *Patient information letter*.

Potential benefits:
Benefits from treatment with eculizumab include a potential decrease in brain injury (from early brain injury and delayed cerebral ischemia) and hereby a better prognosis.

Contacts

Public
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3508 GA

NL
Scientific
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3508 GA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1) Confirmed aneurysmal subarachnoid hemorrhage (SAH)
2) Admission to either the UMCU or Erasmus MC within 11.5 hours after ictus
3) Age 18 years and older

Exclusion criteria

1) Life expectancy < 10 days;
2) Pregnant or breast-feeding women;
3) Participation in another clinical therapeutic study;
4) History of splenectomy or asplenia (potentially increased risk of meningococcal infection);
5) Hematologic malignancy;
6) Patients receiving chemotherapy;
7) Patients who will undergo or underwent an organ transplantation;
8) Patients with myasthenia gravis, glucose-6-phosphate dehydrogenase (G6PD) deficiency, or tuberculosis;
9) Patients who are or will be treated by plasmapheresis or hemodialysis;
10) Patient with a creatinine clearance of <30 or serum creatinine levels

of >169 µmol/l
11) Patients with a known hereditary complement deficiency;
12) Patients allergic to eculizumab, proteins derived from mouse products or other monoclonal antibodies;
13) Patients allergic to (prophylactic) antibiotic treatment for Neisseria meningitidis (quinolones or ceftriaxone (therapeutic));
14) If on admission, it is likely that the aneurysm can only be treated with extracranial-intracranial bypass surgery;
15) If based on head imaging, it will be unlikely that CSF can be obtained 48-72 hours after ictus;
16) Patients with an ongoing infection on admission which is not appropriately treated;
17) Patients who were treated >4 times with antibiotics during the last year;
18) Patients on immunosuppressive therapy.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	05-10-2018
Enrollment:	40
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	SOLIRIS
Generic name:	Eculizumab

Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	10-01-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	13-06-2018
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	24-01-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-02-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	13-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	21-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-03-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	11-04-2019
Application type:	Amendment
Review commission:	METC NedMec

Approved WMO Date:	25-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	27-08-2019
Application type:	Amendment
Review commission:	METC NedMec

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	EUCTR2017-004307-51-NL
CCMO	NL63723.041.17

Study results

Date completed:	16-08-2021
Results posted:	19-02-2024
Actual enrolment:	26

First publication
19-02-2024