Complement Inhibition: Attacking Overshooting inflammation @fter Subarachnoid Hemorrhage (CIAO@SAH trial)

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This study has been transitioned to CTIS with ID 2025-520540-15-00 check the CTIS register for the current data. Primary Objective: To determine the safety and efficacy of 6000 IU C1-INH in patients with subarachnoid hemorrhage (SAH)Primary…

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

Summary

ID

NL-OMON51205

Source
ToetsingOnline

Brief title
CIAO@SAH

Condition

- Central nervous system vascular disorders

Synonym
Hemorrhagic stroke

Research involving
Human

Sponsors and support

Primary sponsor: Haaglanden Medisch Centrum

Source(s) of monetary or material Support: Sint Jacobusstichting Haaglanden Medisch Centrum,Takeda

Intervention

Keyword: Clinical trail, Complement system, Inflammation, Subarachnoid Hemorrhage

Outcome measures

Primary outcome

Efficacy:

To assess efficacy of C1-INH in SAH patients, the difference of delayed cerebral ischemia (DCI) will be analysed between the treatment groups. The criteria consisted of either a new focal neurological impairment (such as hemiparesis, aphasia, apraxia, hemianopia, or neglect), or a decrease of at least 2 points on the Glasgow Coma Scale (either on the total score or on one of its individual components). This should last for at least 1 hour, is not apparent immediately after aneurysm occlusion, and cannot be attributed to other causes by means of clinical assessment, CT or MRI scanning of the brain, and appropriate laboratory studies (e.g. hydrocephalus or rebleeding).

Safety:

As this is a phase II study, we use a primary safety endpoint in addition to our primary efficacy endpoint. This safety endpoint is the patient's rate of complications during hospitalization. This percentage includes adverse events (including serious adverse events) that may be related to study medication. This includes, but is not limited to, venous thromboembolic events, hypersensitivity reactions, hyperglycaemia, sepsis, mortality. Events are

listed by adverse event type, grade, and severity. Patients are assessed daily for these complications by a blinded doctor / nurse. Vital signs are closely monitored and potential side effects of the experimental treatment will be immediately noted in the ICU.

Secondary outcome

Secondary outcomes will be measured during hospitalization and follow-up.

During hospitalization:

- Cerebral infarction on brain CT at 14 days
- Mortality
- Daily neurological condition measured by GCS during the first 14 days
- Complement activity in serum and CSF
- Inflammatory markers in serum and CSF
- Coagulation cascade activation
- ICU length of stay, ventilator days

At discharge:

- Hospital length of stay
- Hospital disposition
- Modified Rankin Scale (mRS Score)
- Glasgow Outcome Score extended (GOSE)
- Barthel Index (BI)
- Montreal Cognitive Assessment (MoCA)
- Quality of life (EQ-5D-5L)

During follow-up at 6 months:

- Modified Rankin Scale (mRS Score)

- Glasgow Outcome Score extended (GOSE)

- Barthel Index (BI)

- Modified Telephone Interview for Cognitive Status (TICS-M)

- Quality of life (EQ-5D-5L)

Study description

Background summary

Aneurysmal subarachnoid hemorrhage (SAH) can lead to devastating outcomes for patients, like cognitive decline. This is caused by early brain injury (EBI) followed by delayed cerebral ischemia (DCI). Neuroinflammation, triggered by the complement system, has been investigated to be a key mediator in the pathophysiology of EBI and DCI. Inhibiting of the complement system is therefore considered to be a potentially important new treatment for SAH. In this study we will investigate the safety and efficacy of C1-inhibitor Cinryze, an approved inhibitor of the complement system, compared to placebo in patients with SAH. By temporarily blocking the complement system we hypothesize limitation of delayed cerebral ischemia and a more favourable clinical outcome for SAH patients due to a decrease in the inflammatory response.

Study objective

This study has been transitioned to CTIS with ID 2025-520540-15-00 check the CTIS register for the current data.

Primary Objective: To determine the safety and efficacy of 6000 IU C1-INH in patients with subarachnoid hemorrhage (SAH)

Primary hypothesis: The hypothesis is that random assignment to C1-INH in SAH will lead to a reduction in delayed cerebral ischemia (DCI) compared to random assignment to placebo. Furthermore, to access safety, no difference should be detected in complication rate during hospitalization between the two groups

Secondary Objective: To determine differences between C1-INH and placebo treatment in the following outcomes for patients with SAH:
- Clinical outcomes: cerebral infarction on brain CT/MRI, mortality, hospital and ICU length of stay, ventilator days, hospital disposition, functional outcome (mRS, GOSE and BI), cognitive function (MoCA/TICS-M) and

quality of life (EQ-5D-5L)
- Neurological damage: BANYAN (GFAP/UCHL-1) blood biomarker
- Complement activation: human serum (WIESLAB assay), total terminal complement activity levels (CH50) and protein levels of complement component (C3b/C, C4b/C and C5b-9) in plasma and CSF
- Coagulation cascade activation (PT, aPPT, PLT, D-dimer, fibrinogen)
- Inflammatory markers in serum and CSF (TNF-alpha, intraleukin)
- Level of C1-inhibitor activity in plasma and CSF

Study design

The proposed trial is a prospective, multicenter, randomized, double-blind, placebo-controlled phase II trial, with one group receiving one dose of C1-INH intravenously (IV) and one group receiving a placebo injection IV. The study will be performed in Haaglanden Medical Center and Amsterdam University Medical Center. During a two-year period, patients diagnosed with SAH on admission to the emergency departments will be eligible for inclusion. If informed consent can be obtained within 12 hours after ictus, patients are randomly assigned to one of the two study arms and will receive a single dose of 6000 IU C1-INH or placebo IV. (1 IU = the average endogenous level C1-esterase inhibitor in 1 ml human plasma). Neither the participants, nor the experimenters will know who is receiving the C1-INH or placebo. All patients will receive standard care. Blood and CSF samples (CSF when an external ventricular drain (EVD) is placed) will be taken from both patient groups before administration of C1-INH or placebo. Additional blood samples will be taken at 6, 12, 24, 48, 72, 96 hours after dosing of the C1-INH or placebo. An additional CSF sample will be taken at 24 hours after dosing of the C1-INH or placebo if a EVD is placed. The timing of these samples is based on the estimated activity and elimination time of the test compound and the timing of the onset of neuroinflammation and complement activation described in previous literature. Blood and CSF samples will be used to measure qualitative levels of functional classical, MBL and alternative complement pathways in human serum, total terminal complement activity levels, protein levels of complement component using different assays and additional inflammatory markers like TNF-alpha and intraleukin. Patients will receive routine CT scans as part of the standard care.

Clinical scores routinely used in the standard clinical care and follow-up during recovery of SAH will be registered up six months after ictus as part of the standard follow-up for SAB.

Informed/deferred consent must be obtained within 12 hours as the efficacy of the C1-INH is suspected to be limited 12 hours after ictus. The HMC will function as a data coordination and analysis center. All neurosurgeons, intensive care physicians/nurses and other people concerned will be instructed with regard to the study.

Intervention

- Cinryze (6000 IU): Cinryze is a C1 esterase inhibitor derived from human plasma. The primary function of Cinryze is to regulate the activation of the complement pathways. This regulation is done by inactivation of Cl which prevents Cir and Cis from binding. These two enzymes are required for activation of the classical complement pathway. In addition, it regulates the intrinsic coagulation pathway through inactivation of kallikrein and factor XIIa. Without this inhibitor, activation of these pathways leads to the production of peptide bradykinin. Therefore, Cinryze is approved for the treatment of angioedema attacks in adults and children with hereditary angioedema (HAE). This is a hereditary disease in which swelling develops attack-like. There is currently no indication for Cinryze in patients with subarachnoidal haemorrhage (SAH). This study will determine whether Cinryze suppresses the complement system enough. With good results, further brain damage and serious unforeseen events in the treatment of future patients with subarachnoid hemorrhage (SAH) can be prevented.

- Placebo: 0.9% NaCl in the same dose as Cinryze

Study burden and risks

The treatment itself consists out of a single intravenous injection (6000 IU) C1-INH or equal injection volume of placebo (physiological saline. C1-INH is a C1 esterase inhibitor isolated from human plasma. As such it is a *human blood product* and cannot be used by people sensitive for human blood products. When medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses and other pathogens. Nevertheless, this risk is considered very low. The risks associated with short term complement inhibition by C1-INH are a theoretical increase in susceptibility for bacterial meningitis. This is controlled in this study by the short term of the treatment with complement inhibitors and careful monitoring of the patient for such infections. This risk is considered low. A decrease in coagulation time because of C1-INH treatment is possible. This can result in thrombosis and might pose extra risks in patients with indwelling catheters. Since the drug is given only once this risk is considered low and patients with a known history of thrombosis will be excluded. The safety profile of C1-INH has widely been investigated in different clinical trials and is excellent.

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

- Confirmed diagnosis of aneurysmal subarachnoid hemorrhage on CT-scan
- Age >= 18 years on admission
- WFNS grade 1-5

Exclusion criteria

- Subarachnoid hemorrhage deemed most likely to *peri mesencephalic* origin after consideration of history, clinical examination and radiological findings (including angiographic imaging);
- Subarachnoid hemorrhage deemed most likely of post-traumatic origin after consideration of history, clinical examination and radiological findings (including angiographic imaging);
- Participation in another clinical therapeutic study;
- Patients with definite infaust prognosis on arrival and/or expected death within 24 hours of admission;
- Patients with a known hereditary complement deficiency (including hereditary angioedema);

- Patients with a history of sensibility to blood products or C1-inhibitor;
- Patients with a history of thrombosis (when known at time of inclusion);
- Pregnant woman.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Pending
Start date (anticipated):	01-10-2023
Enrollment:	128
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	C1-esterase inhibitor
Generic name:	Cinryze
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	10-03-2021
Application type:	First submission

Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	02-07-2021
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	11-01-2024
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	CTIS2025-520540-15-00
EudraCT	EUCTR2020-005731-67-NL
CCMO	NL76082.058.20