Anakinra in Cerebral haemorrhage to Target secondary Injury resulting from Neuroinflammation - a phase II clinical trial

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This study has been transitioned to CTIS with ID 2024-517230-17-00 check the CTIS register for the current data. To determine the effect of anakinra on the development of perihematomal oedema, compared to standard medical management. In an…

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Central nervous system vascular disorders
Study type	Observational invasive

Summary

ID

NL-OMON52254

Source
ToetsingOnline

Brief title
ACTION

Condition

- Central nervous system vascular disorders

Synonym
Cerebral hemmorhage, hemorrhagic stroke

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum

Source(s) of monetary or material Support: Hartstichting,Swedish Orphan Biovitrum AB

Intervention

Keyword: Anakinra, Inflammation, Intracranial hemorrhage, Stroke

Outcome measures

Primary outcome

Primary outcome is effect anakinra compared to standard medical care on perihematomal oedema (measured as oedema extension distance on MRI at day 7). Secondly, we will compare the effect on oedema extension distance of the high dose versus the low dose anakinra groups.

Secondary outcome

Secondary study parameters are to determine whether anakinra alters the level of serum inflammation markers and the blood barrier leakage Ktrans as measured with DCE-MRI on day 7. Furthermore to determine the safety profile of anakinra in sICH and to test whether it influences the clinical outcome in sICH at 90 days.

Study description

Background summary

Spontaneous intracerebral haemorrhage yearly affects over 6000 patients in the Netherlands. It is the deadliest stroke subtype, with a 30-day case-fatality of 40%. Of patients surviving, only few gain independence. However, effective treatment options are still lacking. This is reflected in the prognosis which has not improved over the last 30 years. Inflammation is known to play a vital role in the development of secondary brain injury related to intracranial haemorrhage. The release of blood products in the brain parenchyma leads to an activation of the immune system. This subsequently leads to destruction of the blood brain barrier and the formation of perihematomal oedema. Among the released cytokines, interleukin 1 beta (IL-1β) has a pivotal role. IL-1β is

antagonized by the naturally occurring interleukin-1 receptor antagonist (IL-1Ra) through competitive binding to the IL-1 receptor. Recombinant human IL-1Ra (anakinra) is available for treatment of rheumatoid arthritis, other inflammatory diseases and has been studied in acute sepsis. We hypothesize that anakinra safely reduces SBI after sICH, and that is effect is dose-dependent.

Study objective

This study has been transitioned to CTIS with ID 2024-517230-17-00 check the CTIS register for the current data.

To determine the effect of anakinra on the development of perihematomal oedema, compared to standard medical management. In an exploratory analysis, we will investigate whether this effect is dose-dependent. Furthermore, to study its effect on serum inflammatory markers, increased blood-brain-barrier leakage and functional outcome in patients with sICH.

Study design

Multicentre, prospective, randomized, three-armed (1:1:1) trial with open label treatment and blinded end-point assessment (PROBE design) of IL-1Ra (anakinra).

Intervention:
Patients will receive anakinra in either a high dose (loading dose 500mg i.v., followed by infusion with 2mg/kg/h over 3 days) or in a low dose (loading dose 100mg s.c., followed by subcutaneous administration of 100mg twice a day for 3 days), started within 8 hours of symptom onset. The control group will receive standard medical management.

Study burden and risks

IL-1Ra has been evaluated in many clinical trials and is well tolerated with a consistent safety profile. Treatment duration will just be 3 days, therefore avoiding the risks associated with longterm use of anakinra such as neutropenia and increased infection risk. Patients will be treated in a clinical setting on a specialized stroke unit where they can be monitored frequently. During the first 7 days of this study protocol patients will undergo blood sample collection (day 0, 1, 3 and 7) and a DCE-MRI-scan (day 7±1) which includes administration of gadolinium-based contrast (duration ±40 minutes). The risk of these procedures are negligible and the burden is considered low. Functional outcome at 3 months will be assessed via telephone. Taken together, we expect the risk and burden of participation for individual patients to be low. As we hypothesize that IL-1Ra could ameliorate perihaematomal oedema, which is associated with a poor functional outcome, individual patients might benefit from participation in this trial. Furthermore, this study will contribute to important insights into the therapeutic potential of anakinra in sICH and its

safety profile on group level.

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

1. Age >= 18 years;
2. Supratentorial non-traumatic ICH confirmed by CT, without a confirmed causative lesion on admission CT-angiography (e.g. aneurysm, AVM, DAVF, cerebral venous sinus thrombosis) or other known underlying lesion (e.g. tumour, cavernoma);
3. Minimal intracerebral haemorrhage volume of 10 mL
4. Intervention can be started within 8 hours from symptoms onset;
5. Patient*s or legal representative*s informed consent.

Exclusion criteria

1. Severe ICH, unlikely to survive the first 72 hours (defined as Glasgow Coma Scale score < 6 at time of consent);
2. Confirmed or suspected haemorrhagic transformation of an arterial or venous infarct;
3. Planned neurosurgical haematoma evacuation;
4. Severe infection at admission, requiring antibiotic treatment;
5. Known active tuberculosis or active hepatitis;
6. Use of immunosuppressive or immune-modulating therapy at admission (see 15.1 Appendix A);
7. Neutropenia (Absolute Neutrophil Count (ANC) <1.5 x 109/L);
8. Pre-stroke modified Rankin Scale score >= 3;
9. Pregnancy or breast-feeding;
10. Standard contraindications to MRI;
11. Known prior allergic reaction to gadolinium contrast or one of the constituents of its solution for administration;
12. Known allergy to anakinra or other products that are produced by DNA technology using the micro-organism E. coli;
13. Vaccinations with live attenuated microorganisms within the last 10 days prior to this ICH;
14. Severe renal impairment (eGFR <30ml/min/1.73m);
15. Known active malignancy

Study design

Design

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

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	27-09-2022

Enrollment:	75
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Kineret
Generic name:	anakinra
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	16-03-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	21-03-2022
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-07-2022
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-09-2023
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	CTIS2024-517230-17-00
EudraCT	EUCTR2021-000324-36-NL
ClinicalTrials.gov	NCT04834388
CCMO	NL76607.091.21