AN OPEN-LABEL CLINICAL TRIAL OF INTRA-ARTERIAL MICROPLASMIN ADMINISTRATION IN PATIENTS WITH ACUTE INTRACRANIAL VERTEBROBASILAR ARTERY OCCLUSION

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To evaluate the safety and the arterial recanalization potential of microplasmin when administered intra-arterially in patients with acute intracranial vertebrobasilar artery occlusion.

Ethical review	Approved WMO
Status	Will not start
Health condition type	Embolism and thrombosis
Study type	Interventional

Summary

ID

NL-OMON31313

Source
ToetsingOnline

Brief title
MITI-IA

Condition

- Embolism and thrombosis

Synonym
Acute ischemic stroke, closed cerebral blood vessel

Research involving
Human

Sponsors and support

Primary sponsor: Thrombogenics
Source(s) of monetary or material Support: Biotech bedrijf: ThromboGenics

Intervention

Keyword: Acute, Ischemic, Stroke, Vertebrobasilar

Outcome measures

Primary outcome

EFFICACY:

Proportion of patients achieving recanalization of the basilar artery.

SAFETY parameters:

-Intracranial hemorrhage

-Major bleeding

-Bleeding other than major

-Reocclusion at 48 hr after initiation of study drug (as determined by CT

angiography)

-Serious and non-serious adverse events

-Allergic reactions

-Immunology (Microplasmin and Staphylokinase antibody assays)

-Laboratory data

-Markers of systemic lysis and complement activation

Secondary outcome

EFFICACY:

-Duration of study drug administration to achieve recanalization

-Proportion of patients achieving TIMI 3 and TIMI 2 or 3 grade at the end of

study drug administration

-Clinical outcome as assessed by survival and neurologic rating scales at 7

days, 30 and 90 days post-treatment.

ADDITIONAL:

-Pharmacokinetic measurements.

-Pharmacodynamic measurements (α2-antiplasmin).

Study description

Background summary

Intracranial vertebrobasilar artery occlusion is a form of stroke associated with particularly high mortality (> 75%) and morbidity (those patients that survive are generally extremely debilitated, often with locked-in syndrome)1. Given this grave prognosis, aggressive attempts at anticoagulation/thrombolysis are warranted in patients with acute vertebrobasilar artery occlusion. While the majority of thrombolysis trials have evaluated the middle cerebral artery circulation, the positive results with IV thrombolysis (within 3 hours of symptom onset) and IA thrombolysis (within 6 hours of symptom onset) in MCA territory stroke support the use of thrombolysis in the setting of vertebrobasilar artery occlusion.

All available thrombolytic agents are associated with an increased risk of bleeding, due to systemic effect of the thrombolytic. However, plasmin or derivatives thereof, which are thrombolytic when administered at the site of thrombosis but are rapidly neutralized in the systemic circulation by alpha-2-antiplasmin, are expected to be devoid of such systemic bleeding complication. This hypothesis is supported by preclinical experiments with both plasmin and microplasmin.

Microplasmin has not demonstrated neurotoxicity and has, in several pharmacology experiments, demonstrated neuroprotective characteristics independent from its thrombolytic activity. Unlike available thrombolytic agents, Microplasmin has a direct effect, thereby potentially allowing for more rapid recanalization.

In Preclinical pharmacology, acute stroke models have generally demonstrated that intravenous microplasmin is associated with a reduction in infarct size compared to placebo. In other thromboembolic models in which microplasmin was administered locally at the site of the thomboembolus, a clear thrombolytic effect of microplasmin was observed.

Study objective

To evaluate the safety and the arterial recanalization potential of microplasmin when administered intra-arterially in patients with acute intracranial vertebrobasilar artery occlusion.

Study design

Open-label, multi-centre trial. Single dose regimen.

Clinical outcome will also be assessed at 7, 30 and 90 days days post-treatment. At each of these visits, physical and neurological assessments will be performed.

The trial will investigate a single dose of microplasmin administered intra-arterially as an infusion to patients with acute intracranial vertebrobasilar artery occlusion; an infusion of 1 mg/kg will be administered over 15 minutes followed by a further infusion of 1 mg/kg over 60 minutes.

The planned sample size for the trial is approximately 20 patients.

Intervention

Intra-arterial administration by a catheter and micro-catheter of Microplasmin at the site of thrombotic occlusion.

Dose level:
A single dose regimen will be evaluated; a bolus of 1mg/kg will be administered over 15 mins followed by an infusion of 1mg/kg over one hour. Study drug will be administered intra-arterially (at the site of the thrombotic occlusion).

Concomitant therapy:
Vitamin-K antagonists or heparin (or heparin-like compounds) which results in either an INR>1.4 or an aPTT>2 times control, respectively are prohibited. Administration of an intra-arterial or systemic thrombolytic therapy within the 7 days prior to the study is prohibited. GPIIb/IIIa antagonists or more than one dose of low molecular weight heparin within 48 hours prior to enrolment are prohibited. tPA (or other thrombolytic agents), heparin or heparin-related products, direct-thrombin inhibitors and GPIIb/IIIa antagonists are prohibited from the time of enrolment until 24 hours after study drug administration,

except where study drug is discontinued due to treatment failure.

Study burden and risks

Intracranial vertebrobasilar artery occlusion is a form of stroke associated with particularly high mortality (> 75%) and morbidity (those patients that survive are generally extremely debilitated, often with locked-in syndrome)1. Given this grave prognosis, aggressive attempts at anticoagulation/thrombolysis are warranted in patients with acute vertebrobasilar artery occlusion.

All available thrombolytic agents are associated with an increased risk of bleeding, due to systemic effect of the thrombolytic. However, plasmin or derivatives thereof, which are thrombolytic when administered at the site of thrombosis but are rapidly neutralized in the systemic circulation by alpha-2-antiplasmin, are expected to be devoid of such systemic bleeding complication. This hypothesis is supported by preclinical experiments with both plasmin and microplasmin.

Microplasmin has not demonstrated neurotoxicity and has, in several pharmacology experiments, demonstrated neuroprotective characteristics independent from its thrombolytic activity. Unlike available thrombolytic agents, Microplasmin has a direct effect, thereby potentially allowing for more rapid recanalization.

As microplasmin has not yet been administered to enough patients with acute stroke, the safety and efficacy of microplasmin in acute stroke is unknown at present.

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. New neurologic signs in the vertebrobasilar artery distribution allowing initiation of study drug treatment within 24 hours of the onset of neurological symptoms (loss of consciousness, dysarthria, anarthria, hemianopia, tetraparesis, tetraplegia, bilateral Babinski sign, dysphagia, double vision, nystagmus); other non-specific neurological symptoms such as dizziness, headache, vomiting, nausea are not restricted to the 24 hour time window
2. Patients with angiographically documented vertebrobasilar artery occlusion
3. Age 18-75 (inclusive).
4. Women of child-bearing potential must have a negative pregnancy test prior to enrolment and be using a reliable form of contraception
5. For conscious patients, prior to inclusion in the study and following a full explanation of the nature and purpose of the study, the patient or the patient*s legal representative must consent/assent to participate by signing the Informed Consent document.

Exclusion criteria

1. Patients with coma >6 hrs duration and complete loss of brain stem reflexes (corneal reflex, gag reflex, VOR, pupil reflexes) as measured at the last assessment before sedation/intubation
2. Rapidly improving neurologic signs at any time before initiation of study drug administration.
3. Known contrast agent-sensitivity
4. Uncontrolled hypertension defined as a systolic blood pressure > 180 mm Hg or a diastolic blood pressure > 100 mm Hg on 3 separate occasions at least 10 minutes apart or requiring continuous IV therapy.
5. History of stroke within the previous 6 weeks.
6. Seizures at any time between stroke onset to planned initiation of study drug.
7. History of intracranial hemorrhage

8. History of surgery, lumbar puncture, biopsy or trauma to internal organs within the previous 30 days.
9. Head trauma within the previous 90 days.
10. Known bleeding diathesis.
11. Baseline INR >1.7 or baseline APTT > 2 times normal
12. Baseline platelet count < 100 X 10 9/L.
13. Hypodensity on CT or diffusion abnormality on MRI of greater than half the brain stem
14. Blood glucose > 400mg/dl
15. Patients who have received intra-arterial or systemic thrombolytic therapy within the 7 days prior to the study.
16. Patients who have received tPA or any other thrombolytic agent for the qualifying stroke.
17. Patients receiving vitamin-K antagonists or heparin which results in either an INR>1.4 or an aPTT>2 times control (ULN for the hospital laboratory), respectively. 18. Patients who have received glycoprotein IIb/IIIa inhibitors within 48 hours prior to enrolment.
19. Patients who have received more than one dose of low molecular weight heparin within 48 hours prior to enrolment.
20. Participation in another study with an investigational drug or device within the previous 30 days, prior participation in the present study, or planned participation in another trial within the timeframe of the current trial
21. Life expectancy <3 months
22. Other serious illness that in the opinion of the investigator may confound clinical assessment (eg hepatic, cardiac, or renal failure, advanced cancer)

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Will not start
Start date (anticipated):	01-06-2007
Enrollment:	4
Type:	Anticipated

Medical products/devices used

Product type:	Medicine
Brand name:	nvt
Generic name:	Microplasmin

Ethics review

Approved WMO Date:	06-09-2007
Application type:	First submission
Review commission:	CCMO: Centrale Commissie Mensgebonden Onderzoek (Den Haag)
Approved WMO Date:	24-12-2007
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	EUCTR2005-001075-35-NL
CCMO	NL16933.100.07