INTERVENTIONAL MANAGEMENT OF STROKE TRIAL CLINICAL PROTOCOL - IMS III

A phase III, randomized, multi-center, open label, 900 subject clinical trial that will examine whether a combined intravenous (IV) and intra-arterial (IA) approach to recanalization is superior to standard IV rt-PA (Activase®/Actilyse®) alone when initiated within three hours of acute ischemic stroke onset.

Published: 27-12-2010
Last updated: 04-05-2024

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

Summary

ID

NL-OMON36365

Source
ToetsingOnline

Brief title
IMS III

Condition

- Central nervous system vascular disorders
- Embolism and thrombosis

Synonym
ischemic cerebrovascular accident, Stroke

Research involving
Human

Sponsors and support

Primary sponsor: National Institute of Health
Source(s) of monetary or material Support: US National Institutes of Health represented by the University of Cincinnati;USA

Intervention

Keyword: combined intravenous (IV) and intra-arterial (IA) approach, Ischemic Stroke, recanalization, rt-PA (Actilyse®)

Outcome measures

Primary outcome

To determine if ischemic stroke subjects with a baseline NIH Stroke Scale Score

>= 10 (8-9 with positive CTA)

treated with recombinant tissue plasminogen activator (rt-PA; [Alteplase

recombinant], Actilyse® Boehringer

Ingelheim) utilizing a combined intravenous plus intra-arterial (IV/IA)

approach to recanalization started within

3 hours of onset, are more likely to have a favorable outcome at 3 months,

defined as a modified Rankin score of

0-2, as compared to subjects treated with standard IV rt-PA alone.

Secondary outcome

1. To compare the safety of a combined IV/IA approach to IV rt-PA alone. The primary measures of safety will be mortality at 3 months and occurrence of treatment-related symptomatic intracranial hemorrhage (ICH) confirmed within 24 hours.

2. To evaluate the effectiveness of a combined IV/IA approach as compared to standard IV rt-PA by a number of secondary outcome measures.

3. To determine the cost effectiveness of the combined IV/IA approach as compared to standard IV rt-PA as measured by differences in utilization of resources and quality of life over 12 months between the two arms of the trial

4. To develop and maintain a network of interventional centers to test the safety, feasibility, and potential efficacy of new mechanical devices as part of a combined IV/IA approach to recanalization

Study description

Background summary

Every year approximately 200,000 people in the Netherlands suffer from a stroke, one third of these dies within 12 months. Nearly two thirds of patients who survive a stroke, remain disabled and dependent on help from others. An acute stroke is caused by the interruption of oxygen and nutrients supply to the brain by a local or migrating blood clot. Rapid diagnosis of the clinical symptom complex, speedy transfer of the patient to a hospital specialized on

the treatment of stroke (stroke unit) and the immediate start of an adequate therapy are decisive for the long term outcome.
Primary diagnostic measures in the hospital include a first physical and neurological examination. By techniques such as computer tomography (CT) or Magnetic resonance tomography (MRT) the location and the extent of the stroke can be determined. Within the first three hours after onset of symptoms for ischemic stroke thrombolysis with the Recombinant Tissue Plasminogen Activator (rt-PA, Alteplase) is the approved primary treatment for recanalisation. In the Netherlands rt-PA is licensed under the trade name Actilyse ® and used for thrombolysis systemically (intravenous infusion only) and locally (intra-arterial administration during cerebral angiography).

Study objective

The primary objective of the trial is to determine if ischemic stroke subjects with a baseline NIH Stroke Scale Score (NIHSSS] >= 10 (8-9 with positive CTA) treated with recombinant tissue plasminogen activator (rt-PA; [Alteplase recombinant], Actilyse® Boehringer Ingelheim) utilizing a combined intravenous plus intra-arterial (IV/IA) approach to recanalization started within 3 hours of onset, are more likely to have a favorable outcome at 3 months, defined as a modified Rankin score (mRS) of 0-2, as compared to subjects treated with standard IV rt-PA alone.

Study design

IMS III is an international, multi-center, prospective, randomized, open IIIB - study planning to enrol 900 patients with an ischemic stroke, in whom thrombolytic therapy with Actilyse ® can be started within 3 hours of onset of symptoms. After obtaining written informed consent from the patient or his/her legal representative respectively, the patient will be randomized in a 2:1 ratio to either a combined intravenous / intra-arterial treatment with Actilyse ® or to intravenous thrombolytic therapy only. Patients who are randomized to receive a combination therapy, will first be treated with an intravenous infusion of Actilyse ® at 0.9 mg per kilogram of body weight (max. dose 90 mg) for 60 minutes , followed by an intra-arterial administration of Actilyse ® close to the location of the thrombus during cerebral angiography (supplementary administration of up to 22 mg over 120 min, maximum total dose 112 mg). Patients randomized to the group with intravenous therapy only, get a 60 minutes infusion of 0.9 mg per kilogram of body weight Actilyse ® (max. total dose 90 mg). All patients furthermore receive the usual standard therapy for treatment of an ischemic stroke. The duration of hospitalization of the patient is not extended by participation in the study! All patients will closely be monitored during their hospitalisation. Further follow-up assessements will take place at 1, 3, 6 and 9 months and after one year.

Intervention

The patient*s participation in the trial will last approximately 1 year. During this time it is requested that the study doctor*s instructions are followed. The details of the study are as follows:
• As with all patients who have had a stroke, the patient will undergo a physical and neurological examination and will then be given fluids and rt-PA via a thin tube inserted into a vein in the arm (intravenous infusion).
• Either magnetic resonance imaging (MRI) or computer tomography (CT) is carried out, depending on hospital routine. This produces images of the brain either using a large electromagnet (MRI) or a low dose x-ray machine. This allows the doctor to assess the extent of the stroke.
• Approximately 30 ml blood will be taken from a vein in the patient*s arm for routine laboratory tests on the general blood parameters.
• A previously determined randomization procedure will determine if the patient is to receive the rt-PA as an intravenous/intra-arterial combination treatment or as an intravenous infusion alone. The probability is 2:1, i.e. two out of three patients will be given the intravenous/intra-arterial combination treatment and one will be given the intravenous infusion alone (2: 1 randomisation). You and the study doctor will know at all times which treatment the patient is receiving.
• If the patient is assigned to receive the intravenous rt-PA alone treatment, the rt-Pa infusion that has already been started with a dose of 0.9 mg per kg weight (max. 90 mg in total) is continued. The intravenous administration is finshed after a total of 60 minutes.
• If the patient is assigned to the intravenous/intra-arterial combination treatment with rt-PA, the intravenous infusion is initially continued with 0.9 mg per kg weight (max. 90 mg). The intravenous administration is finshed after a total of 60 minutes. What is known as a cerebral angiogram is then carried out. This is a routine procedure where a contrast agent is used to show the narrowing in the cerebral vessels on an x-ray image. Administration of an additional dose of rt-Pa (up to 22 mg) is then made via a thin plastic tube (catheter) inserted into an artery and advanced directly near the blood clot in the brain. The attending physician can also use additional standard procedures such as gentle ultrasound waves or approved systems to draw out the clot through the inserted catheter.
• To avoid pain and sudden movement of the patient, in accordance with the hospital routine, the patient will receive local anaesthesia for this procedure.
• The patient undergoes regular physical examinations during and after treatment. The pulse and blood pressure are monitored.
• After the treatment another MRI/CT examination is carried out, depending on the clinic's standard routine. After this, what is known as a CTA (computed tomography angiography) is carried out, where an intravenously administered contrast agent can show in an x-ray if the blood clot in the brain has dissolved.
• Further blood tests are carried out (30 ml at 18-30 hours and 5 days after treatment)
• While the patient is in hospital and when the patient is discharged the

attending study staff will ask him/her some questions about how he/she is feeling.
• 7-10 days, 1 month, 6, 9 and 12 months after the treatment the study team will contact the patient and will ask him/her to answer some questions on how he/she is feeling and about any medications the patient is taking at the time.
• 3 months after the treatment the study doctor will ask the patient to come to a check-up. This will involve a physical and neurological examination and the doctor will ask him/her some questions about how he/she is feeling at the time.

Study burden and risks

rt-PA (Actilyse®) has to date been used on several million patients. It is, however, possible that not all side effects and risks have been investigated. A common side effect of the treatment with rt-PA is bleeding, as rt-PA dissolves existing blood clots.
This means that very frequently (in more than one in ten patients) treatment with rt-PA can lead to bruising and bleeding in the region where the needle for the blood sample and the catheter are inserted. Commonly (in more than one in 100 patients) patients may experience nose bleeds or bleeding in the gums, mouth and throat, stomach or intestines, in the skin and blood in urine.
Bleeding in the brain is particularly serious, as this can lead to permanent disability or even death. In patients who have had a stroke with the rt-PA treatment there is a 10% risk, i.e. one in 10 patients can suffer from bleeding in the brain. It could be that the risk with a combined intravenous/intra-arterial administration of rt-PA in association with invasive measures, such as removing a blood clot during a cerebral angiography, is slightly higher than with intravenous administration alone. In earlier studies on combined intravenous/intra-arterial application approximately 4% of patients (4 in 100 patients) needed blood or blood product transfusions.
Rarely (in fewer than one in 1000 patients) there can be bleeding in the liver, lungs or eyes with rt-PA.
An allergic reaction to rt-PA is also possible (in more than one in 1000 patients). This can manifest in the form of a rash (hives), itching all over the body or shortness of breath. Very rarely (in fewer than 1 in 10,000 patients) the patient may go into anaphylactic (allergic) shock, which can be serious or even fatal.
Other possible rare side effects include:
A drop in blood pressure, changes in the heart frequency, nausea, vomiting, elevated body temperature
Further risks:
The study doctor will explain the possible risks of routine cerebral angiography in detail and will ask the patient to sign a standardised consent form. One specific point to note is that during the routine cerebral angiogram a contrast agent is injected into the catheter which shows the vessels in the brain in the x-ray during the examination. This contrast agent can slightly affect kidney function. In 2 to 4 out of 100 patients the contrast agent can trigger a mild allergic reaction; such as pins and needles, a rash, hot flushes

and feeling unwell. Severe allergic reactions such as breathlessness can occur in one in 1000 patients. Radiation exposure during the standard angiography and routine check-ups is very low. There is also always a low risk that the catheter will damage a blood vessel, cause vessel spasm or that other blood vessels are blocked by parts of the blood clot that are released or parts of the catheter. These complications can occur in 3-5% (3 to 5 in 100 patients) of cases during routine cerebral angiography. In previous studies on combined intravenous/intra-arterial therapy with rt-PA these complications occurred in less than 3%.
At the sites where blood is taken pain, burning, swelling, bleeding, blood clots, pallor and rarely inflammation or nerve damage can occur. Overall, no more than 90 ml of blood will be drawn from the patient during the course of the study.
As undesirable side effects on a foetus or embryo cannot be ruled out, pregnant women or women who may become pregnant and breast feeding women cannot take part in this trial.
During the trial patients will be closely monitored in case of any side effects. If there is a problem the patient will immediately receive appropriate treatment. It is also necessary that the patient does inform the study doctor about any health problems, health impairment or impaired well-being he/she experiences during the trial, even if he/she thinks it unlikely that it is connected to receiving the study preparation. The study doctor will decide on suitable measures to take. An independent expert group will also constantly monitor the safety of the study and side effects of the study medication for the entire study duration.Both the exclusively intravenous administration of rt-PA and the combined intravenous/intra-arterial administration of this drug have beneficial outcomes in the treatment of stroke patients. The investigators hope that they can further improve the treatment of stroke patients with the results of this trial to compare these two forms of application. Even if it cannot be guaranteed that the patient will benefit from taking part in this trial, the experience gained by his/her participation could be very beneficial for future stroke patients. Therefore the risk:benefit assessment for this trial is positive.

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

• Age: 18 through 82 years (i.e., candidates must have had their 18PthP birthday, but not had their 83rd birthday).
• Initiation of IV rt-PA within 3 hours of onset of stroke symptoms. Time of onset is defined as the last time when the patient was witnessed to be at baseline (i.e., subjects who have stroke symptoms upon awakening will be considered to have their onset at beginning of sleep).
• An NIHSSS >= 10 at the time that IV rt-PA is begun or an NIHSSS >7 and <10 with an occlusion seen in M1, ICA or basilar artery on CTA at institutions where baseline CTA imaging is standard of care for acute stroke patients.
• Investigator verification that the subject has received/ is receiving the correct IV rt-PA dose for the estimated weight prior to randomization

Exclusion criteria

• History of stroke in the past 3 months.
• Previous intra-cranial hemorrhage, neoplasm, subarachnoid hemorrhage, or arteriovenous malformation.
• Clinical presentation suggests a subarachnoid hemorrhage, even if initial CT scan is normal.
• Hypertension at time of treatment; systolic BP > 185 or diastolic > 110 mm Hg; or aggressive measures to lower blood pressure to below these limits are needed.
• Presumed septic embolus, or suspicion of bacterial endocarditis
• Presumed pericarditis including pericarditis after acute myocardial infarction.
• Suspicion of aortic dissection
• Recent (within 30 days) surgery or biopsy of parenchymal organ.

• Recent (within 30 days) trauma, with internal injuries or ulcerative wounds.
• Recent (within 90 days) severe head trauma or head trauma with loss of consciousness.
• Any active or recent (within 30 days) hemorrhage.
• Patients with known hereditary or acquired hemorrhagic diathesis, coagulation factor deficiency; or oral anticoagulant therapy require coagulation lab results prior to enrollment. Any subject with INR greater than 1.7 or institutionally equivalent prothrombin time is excluded. Patients without history or suspicion of coagulopathy do not require INR or prothrombin time lab results to be available prior to enrollment.
• Females of childbearing potential who are known to be pregnant and/or lactating or who have positive pregnancy tests on admission.
• Baseline lab values: glucose < 50 mg/dl or > 400 mg/dl, platelets <100,000, or Hct <25
• Patients that require hemodialysis or peritoneal dialysis, or who have a contraindication to an angiogram for whatever reason.
• Patients who have received heparin or a direct thrombin inhibitor (Angiomax*, argatroban, Refludan*, Pradaxa) within the last 48 hours; must have a normal partial thromboplastin time (PTT) to be eligible.
• Subjects with an arterial puncture at a non-compressible site or a lumbar puncture in the previous 7 days.
• Patients with a seizure at onset of stroke
• Patients with a pre-existing neurological or psychiatric disease that would confound the neurological or functional evaluations, mRS score at baseline must be <= 2. This excludes patients who live in a nursing home or who are not fully independent for activities of daily living (toileting, dressing, eating, cooking and preparing meals, etc.)
• Other serious, advanced, or terminal illness.
• Any other condition that the investigator feels would pose a significant hazard to the patient if Activase* /Actilyse® (Alteplase) therapy is initiated.
• Current participation in another research drug treatment.
• Informed consent is not or cannot be obtained. For example, obtunded patients are not automatically excluded from the study. However, if the next of kin or legal guardian (i.e., the individual legally empowered in the state where the consent is obtained) cannot provide consent, randomization and entry into the study could not proceed.;Imaging Exclusion Criteria
• High density lesion consistent with hemorrhage of any degree.
• Significant mass effect with midline shift.
• Large (more than 1/3 of the middle cerebral artery) regions of clear hypodensity on the baseline imaging. An ASPECTS of < 4can be used as a guideline when evaluating >1/3 region of territory involvement. Sulcal effacement and / or loss of grey-white differentiation alone are not contraindications for treatment.
• CT evidence of intraparenchymal tumor
. Baseline CTA without evidence of an arterial occlusion. (NOTE: The study does not require baseline CTA imaging, if CTA is routinely performed prior to IV rt-PA lesion information obtained should be used to satisfy this exclusion)

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	12-09-2011
Enrollment:	20
Type:	Actual

Medical products/devices used

Generic name:	Merci Retriever System; SOLITAIRE FR Device
Registration:	Yes - CE intended use
Product type:	Medicine
Brand name:	Actilyse
Generic name:	Alteplase
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	27-12-2010
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

Approved WMO

Date:	21-04-2011
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-12-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-12-2011
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	16-05-2012
Application type:	Amendment
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	EUCTR2009-017454-12-NL
ClinicalTrials.gov	NCT00359424
CCMO	NL34886.100.10