SITS and the European Union License for rt-PA in acute stroke

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**BACKGROUND**

Intravenous treatment with alteplase, a tissue plasminogen activator (t-PA), has now been approved by the European Union (EU) regulatory authorities for the treatment of acute ischaemic stroke within three hours of symptoms onset. Two major conditions were set for this approval. The first condition was that all patients treated with alteplase during a three year period within the EU, Norway and Iceland will be registered in the SITS internet database in accordance with the SITS Monitoring Study (SITS-MOST) protocol. The second condition was that a randomised controlled study of alteplase versus placebo, later called ECASS III (European Co-operative Acute Stroke Study III), should be launched for patients who could be treated within a three to four hour time interval.

SITS has accepted a request to provide the European Medicines Evaluation Agency (EMEA) with biannual reports on the proportions of patients who experience a symptomatic intracranial haemorrhage or die following treatment or who are independent for activities of daily living (ADL) at three months follow up.

Treatment within 3 hours after onset of ischaemic stroke is highly effective, as indicated in the consensus statement of this conference in October 2000\(^1\), which was based on the outcome of eight randomised controlled trials\(^2\)-\(^9\). Intravenous t-PA was approved in US in 1996. Although the indication for this treatment seems widely accepted for patients within three hours of symptoms onset also in Europe, it has been claimed that the results were based on rather few patients included in randomised controlled trials\(^10\). There is also a concern about the risk for symptomatic intracranial haemorrhage caused by the treatment. Since many stroke experts would regard a randomised trial of t-PA versus placebo control within three hours of stroke onset as unethical, such a trial would probably not be feasible\(^11\). Collecting safety and efficacy data through an internet-based register, such as SITS, provides an opportunity to evaluate whether the rate of symptomatic intracranial haemorrhage, death and the proportion
of patients with independence for ADL remains at least at the level of randomised controlled trials or better. The EU regulatory authorities decided that data collected through SITS and data from the randomised controlled trial within the three-four hour time window will form the basis for a final evaluation of continued licence approval after three years. This decision was made by the EU Commission on September 29, 2002 and will have to pass the appropriate national authorities for implementation.

**SITS Monitoring Study (SITS-MOST) and Treatment indications**

A study protocol for the SITS Monitoring Study has been required and approved by EMEA for the purpose of monitoring safety during implementation of thrombolysis in stroke. Several details in the protocol, including the treatment criteria, have been adjusted on request of EMEA.

*Treatment criteria:*

- Female or male inpatients, between 18 and 80 years, with a clinical diagnosis of ischaemic stroke causing a measurable neurological deficit defined as impairment of language, motor function, cognition, gaze, vision and/or neglect. Ischaemic stroke is defined as an event characterised by sudden onset of acute focal neurological deficit, presumed to be caused by cerebral ischaemia, after CT scan exclusion of haemorrhage.

- Onset of symptoms is within 3 hours prior to initiation of thrombolysis treatment. Stroke symptoms must be present for at least 30 minutes and not significantly improve before treatment. Symptoms must be distinguishable from an episode of generalized ischaemia (i.e. syncope), seizure, or migraine disorder.

- Patients are willing to receive thrombolysis treatment and to give informed consent with regard to retrieval of data and follow up procedures, according to the regulations in participating countries.

- Patients are willing and able to comply with the study protocol.
Main Exclusion criteria:

- Evidence of intracranial haemorrhage (ICH) on the computer tomography (CT) and magnetic resonance imaging tomography (MR) scan.
- Minor neurological deficit or symptoms rapidly improving before start of infusion
- Severe stroke as assessed clinically (e.g. NIHSS>25) and/or by appropriate imaging techniques
- Seizure at onset of stroke
- Patients with any history of prior stroke and concomitant diabetes
- Prior stroke within the last 3 months
- Systolic blood pressure >185 mmHg or diastolic blood pressure >110 mmHg, or aggressive management (IV medication) necessary to reduce BP to these limits
- Blood glucose <50 or >400 mg/dl (<3 mmol/l or >22 mmol/l).
- Increased risk of bleeding according to specified list of conditions
- Severe concomitant diseases according to specified list

DATA ENTRY

Data entry includes time of onset of stroke symptoms and arrival at hospital, time for brain imaging and start of treatment, age and gender, initial stroke severity, risk factors, stroke subtype, CT scanning before and after treatment, stroke severity after treatment, evaluation of haemorrhagic or other complication, and Rankin grade at 3 months. Complete data entry takes a few minutes using a ‘point and click’ design. The data entry and feed back reports are illustrated in Fig 1a and b.

CRITERIA FOR PARTICIPATION

The EU approval includes a condition that treatment should be given under the responsibility of a physician trained in neurological care. Criteria for centre participation are specified in the SITS-MOST protocol.
A centre must have solid experience from acute stroke treatment. The physician on call at the emergency must have the authority to initiate thrombolysis treatment or have immediate access to a colleague with this authority.

Figure 1 a: Data flow in SITS Monitoring Study. Entry of data on baseline and demographic factors and treatment outcome generate automatic reports immediately on confirmation of data. Statistical reports on centre data are compared with national and international data.
Figure 1 b: Reports on main outcomes created biannually for European Medicines Evaluation Agency, EMEA, including symptomatic intracranial haemorrhage (SICH), death and independence for activities of daily living (ADL) at 3 months.

During thrombolysis and the first day after admission, patients will be admitted to semi-intensive or intensive care, preferably but not necessarily within the stroke unit, i.e., constant nurse in the room during procedures, qualified to monitor level of consciousness and neurological impairment, and monitoring equipment for blood pressure, pulse rate, ECG, oxygen saturation and body temperature.

The ward responsible for thrombolysis treatment should be specialised in stroke management with a multidisciplinary team including a trained stroke nurse, usually also consisting of physiotherapist, occupational therapist, speech therapist, social worker and a neuropsychologist. The ward should adhere to a policy of early rehabilitation.

**CERTIFICATION OF CENTRES AND USERS**

Centres intending to use intravenous thrombolysis in agreement with the EU approval use an electronic application form on the SITS website, [www.acutestroke.org](http://www.acutestroke.org). In this form each centre, through its local coordinator, accepts the basic conditions for participation in SITS and also confirms that they do fulfil the criteria set up by EMEA and the SITS-MOST protocol. The application is then submitted to the National Coordinator. The National Coordinator then provides the user name and password after approval of the application. Local users are appointed by the local coordinator, who is also authorised to enter usernames and passwords for these.
**MAIN STUDY OUTCOMES**

The main outcomes of the SITS Monitoring Study are symptomatic intracranial haemorrhage (SICH) following haemorrhage, death, and independence for daily living activities at three months. The outcomes of the study will be compared with those of a systematic analysis of randomised controlled trials, which provides a proportion of 8.6% for SICH, 17.3% for death and 50.1% for independence\(^1\). These proportions and their 95% confidence intervals are shown in Table 1.

Table 1. Proportions of symptomatic intracranial haemorrhage (SICH), death and independence for activities of daily living in randomised controlled trials.

| Proportions of SICH, death and independence per 100 patients treated and 95% confidence intervals (CI) in randomised controlled trials |
|---|---|---|
| SICH* (N=465) | Death (N=479) | Independence (N=465) |
| Proportion | 95% CI | Proportion | 95% CI | Proportion | 95% CI |
| 8.6 | 6.1 – 11.1 | 17.3 | 13.9 – 20.7 | 50.1 | 45.6 – 54.6 |

* SICH has been defined differently in various trials. For reasons of consistency we refer to symptomatic parenchymatous haemorrhage type 2 only.

**STUDY COORDINATION**

SITS-MOST will be coordinated at the national level by the National Coordinators and at the international level by the International Coordination Office (ICO) at the Karolinska Hospital in Stockholm. All contact details are available through the home page [www.acutestroke.org](http://www.acutestroke.org).

The SITS-MOST Steering Committee decides about the study protocol and publications released from SITS.

The new SITS database software programming and maintenance is provided by the Uppsala Clinical Research at the Academic Hospital in Uppsala. Contact details are available at the UCR website, [www.ucr.uu.se](http://www.ucr.uu.se).

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