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Techniques in
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Current Indications and Results of Thrombolysis by Intravenous Recombinant Tissue Plasminogen Activator

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A number of landmark trials have proven the efficacy of thrombolysis by intravenous recombinant tissue plasminogen activator in the acute phase of the ischemic stroke. Despite the recently extended time window of 4.5 hours, the number of people who are being treated in most centers is low. Several reasons seem to account for this, including poor recognition of symptoms, delays in emergency transport, low levels of public awareness, or age limits originally imposed by drug regulatory rules. Trials are ongoing to possibly extend the indications to the treatment. A major effort is to extend the time window by bridging the treatment with neuroprotective approaches, or by identifying subgroups that may particularly benefit from recanalization and reperfusion. Procedures using ultrasounds or alternative intravenous compounds are also being investigated with promising results.

Tech Vasc Interventional Rad 15:10-18

KEYWORDS acute ischemic stroke, rt-PA, thrombolysis

Intravenous Thrombolysis

Stroke is the second most common cause of death worldwide and a major cause of disability. Treatments, however, are very limited. Pharmacologic fibrinolysis is the only approved drug therapy for the treatment of acute ischemic stroke. The rationale behind the treatment relies on the demonstration, in various experimental animal models, that early recanalization improves the outcome. Endogenous fibrinolysis activity in humans, however, is often insufficient to resolve vessel occlusions.[1]

Tissue-type plasminogen activator (t-PA) is a thrombolytic drug that lyses fibrin clots through activation of plasminogen to plasmin. Plasmin is a potent proteolytic enzyme that digests fibrin (the main protein component of the clot) into soluble fragments (fibrin degradation products). This process ensures clot dissolution and protects blood flow, particularly in the microcirculation.[2] Recent reports have focused on effects of t-PA that exceed the boundaries of the blood coagulation and fibrinolysis to include tissue remodeling by degradation of extracellular matrix proteins, either directly or through the activation of matrix metalloproteinases,[3,4] or by direct cytotoxicity and increased permeability of the neurovascular unit.[5,6] These aspects typically pertain to research fields and are dismissed in clinical practice. Early attempts to implement thrombolytic medications in the acute stroke go back to the 1970s. The use of streptokinase was consistently unsuccessful because of severe hemorrhagic complications.[7] In the 1980s, recombinant tissue plasminogen activator (rt-PA) was shown to be effective in reducing infarct volume in a rabbit embolic stroke model.[8] Several reports thereafter confirmed the efficacy in different animal models[9,10] and gave support to clinical trials.

A number of landmark trials were thus carried out in the 1990s that established the effectiveness of the treatment in subjects with stroke. In 1995, the study sponsored by the National Institute of Neurological Disorders and Stroke (NINDS) demonstrated that treatment with intravenous (IV) rt-PA within 3 hours from onset of ischemic stroke improves clinical outcome at 3 months. Moreover, one half of the patients were treated within 90 minutes of symptom onset. The 3-month outcomes, modified Rankin Scale (mRS) and Bar-

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1089-2516/12/$-see front matter
doi:10.1053/j.tvir.2011.12.002

Table 1 Major Inclusion and Exclusion Criteria for Treatment With Intravenous rt-PA in Acute Ischemic Stroke

Inclusion criteria
Age 18-80 yr (upper age limit not mentioned by U.S. license and guidelines)
Diagnosis of ischemic stroke causing a measurable neurological deficit
Onset of symptoms within 4.5 h
Exclusion criteria
Clinical
Oral anticoagulant treatment (INR >1.7, required by U.S. license)
Symptoms suggestive of subarachnoid hemorrhage
Previous ICH
Manifest or recent, severe or dangerous bleeding (within 21 d, according to U.S. license)
Arterial puncture at a noncompressible site (within 7 d, according to U.S. license)
Major surgery within 3 mo (within 14 d, according to U.S. license)
Sustained SBP >185 mm Hg or DBP >110 mm Hg (aggressive treatment needed to lower blood pressure, according to European license)
Myocardial infarction within 3 mo (according to U.S. license)
Previous stroke within 3 mo
Combination of previous stroke and diabetes mellitus (according to European license)
Very severe deficits at onset (NIHSS score >25 required by European license)
Minor or rapidly improving neurological deficits
Severe trauma within 3 mo (head trauma only, according to U.S. license)
Seizure at onset
Radiological
Severe stroke demonstrated by brain imaging (involvement of at least one-third of the cerebral hemisphere, according to U.S. license)
Laboratory
Heparin within previous 48 h with elevated current aPTT
Platelets <100,000 per mm^3
Blood glucose level <50 mg/dL (or >400 mg/100 mL, according to European license)

rt-PA, recombinant tissue plasminogen activator; INR, international normalized ratio; ICH, intracranial hemorrhage; NIHSS, National Institutes of Health Stroke Scale; aPTT, activated partial thromboplastin time; SBP, systolic blood pressure; DBP, diastolic blood pressure.

thel Index, favored rt-PA treatment.[11] The European Cooperative Acute Stroke Study (ECASS) I[12] was a randomized, prospective, multicenter, double-blind, placebo-controlled trial. Patients were randomly assigned to receive 1.1 mg/kg IV rt-PA or placebo within 6 hours from symptom onset. Primary outcomes were the Barthel Index and mRS at 90 days. Although the study ended with negative results and suffered from protocol violations, the analysis of a subgroup of patients treated within 3 hours suggested benefit of the treatment.[13] ECASS II had a similar design but differed using a lower dose (similarly administrated within 6 hours of symptom onset) and stricter eligibility criteria, which included imaging and blood pressure guidelines. There was a favorable trend for rt-PA, but results were essentially negative, and symptomatic intracranial hemorrhages (sICH) remained more common in the rt-PA group, although this difference did not lead to an overall increase in morbidity or mortality.[14] The Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke, a phase III, placebo-controlled, double-blind, randomized study, also failed to support the use of rt-PA in patients treated within 3 to 5 hours from symptom onset.[15] In the double-blind NINDS rt-PA Stroke Study, 624 patients were randomized to receive IV rt-PA (0.9 mg/kg, maximum 90 mg) or placebo within 3 hours of stroke symptom onset. Treatment with IV rt-PA was associated with at least 30% increase in the chances of achieving functional independence with complete or nearly complete neurological recovery at 3 months. Efficacy was greatest for patients treated within 90 minutes of symptom onset. Symptomatic intracerebral hemorrhages within 36 hours occurred in 6.4% of the treated patients versus 0.6% of control subjects, without any significant differences in mortality between the groups. Based on the results of the NINDS trials (I and II) in 1996, the Food and Drug Administration approved rt-PA for patients with acute ischemic stroke treated within 3 hours of symptom onset.[11] The dose of rt-PA was 0.9 mg/kg (not to exceed 90 mg in total), to be administered IV over 1 hour, with 10% of the total dose given as a bolus.[16] A pooled analysis from randomized placebo-controlled trials of IV rt-PA (NINDS I and II, ECASS I and II, and Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke A and B) was then performed to test the feasibility of a longer time window. The results were suggestive for a potential benefit beyond 3 hours, although the greater benefit was observed with earlier treatment.[17] The ECASS III trial in 2008 definitely showed a modest, but significant, improvement in the clinical outcome of IV rt-PA infusion within the time window of 4.5 hours.[18] Table 1 reports the major inclusion and exclusion criteria, according to the European and U.S. licenses.

Thrombolysis in Elderly Patients

Despite the recently extended time window of 4.5 hours, the number of people who are being treated in most centers can be as low as 1% to 4% of all eligible patients.[19] Several reasons