

Clinical trials in acute stroke and transcranial colour-coded sonography (TCCS)

G. Malferrari
M. Zedde

Neurology Department, Stroke Unit, Santa Maria Nuova Hospital, Reggio Emilia, Italy
E-mail: Malferrari.Giovanni@asmn.re.it

The rationale for using thrombolysis to treat ischaemic stroke is to obtain recanalisation of the occluded arteries in order to restore brain function of hypoperfused areas, saving tissue at risk. Its justification lies in the knowledge that most ischaemic strokes are produced by arterial occlusions, embolic or thrombotic. Indeed post-mortem histological and angiographic studies demonstrate the presence of occlusive thrombi in up to 80% of ischaemic strokes. The speed of intracranial clot lysis strongly correlates with early neurological improvement, with the extent of the reduction of the ischaemic area, and with a favourable prognosis. Although there is evidence that early recanalisation is one of the most powerful predictors of favourable outcome at 3 months after thrombolytic treatment, it is likely that other factors are also involved in conditioning the prognosis, e.g., some stroke patients show a minimal or no improvement, or a persistent disability, despite rtPA-induced recanalisation.

Several factors, besides the occlusive pattern, are predictors of poor prognosis in stroke patients treated with rtPA. These include:

- Stroke severity
- Older age
- Systolic hypertension
- Extent of hypodensity or brain oedema on pre-treatment CT
- Hyperglycaemia on admission.

The beneficial effect of the early restoration of cerebral flow on long-term outcome may be partially limited by the above-mentioned factors and by changes in systemic arterial pressure during thrombolysis.

Therefore a multimodal approach is needed in order to achieve a more reliable selection of patients for rtPA thrombolysis.

It is suggested by several groups that, if possible, every effort should be made to demonstrate a large-artery intracranial occlusion (by means of the modern neuroimaging techniques) before rtPA administration.

Prompt use of transcranial colour-coded sonography (TCCS) with validated protocols and contrast medium injection could make it possible to sort stroke patients with large artery disease into subgroups homogeneous for site and extent of arterial occlusion, so as to further select those who might most benefit from thrombolysis. Indeed available data point out that, for example, tandem occlusions of the ICA and MCA ± ACA would be the least responsive to thrombolysis and could be candidates for sequential iv-ia thrombolysis or for ia thrombolysis alone. Therefore in patients with an occlusive pattern, promptly diagnosed by TCCS and known for its resistance to iv thrombolysis, such as basilar artery occlusion or MCA occlusion between 3 and 6 hours of symptom onset (especially if there a significant mismatch in PCT or PWI-DWI MR), the local intraarterial approach is suggested. This is what the Italian guidelines (SPREAD 2005-2007) recommend, in accordance with American Heart Association guidelines:

For MCA occlusion patients, angiographically diagnosed and without early infarction signs on basal brain CT, within 6 hours of symptom onset, intraarterial rtPA thrombolysis is suggested, executed in centres with documented interventional neuroradiology experience (Grade 2C).

Endovascular techniques (drug thrombolysis and/or mechanical manoeuvres) are indicated only in centres with well documented experience in interventional neuroradiology, in cases of major arterial trunk occlusion (internal carotid artery, proximal middle cerebral artery, basilar artery) with a clinical picture predicting a high fatality risk or severe functional disability (Grade 2D).

For patients with acute thrombosis of the basilar artery without early signs of infarction on CT/MRI, ia thrombolysis is suggested (Grade 2C).

As regards ia thrombolysis of MCA occlusions, the data derive from rpro-UK studies. PROACT I was a

dose-finding study performed on 40 patients, whereas PROACT II randomised 180 patients (mean NIHSS 17) with angiographically demonstrated MCA occlusion to receive rpro-UK 9 mg followed by heparin bolus 2,000 IU and then 500 IU/hour for 4 hours, or heparin alone, in a ratio of 2:1, within 6 hours of symptom onset; the results were an increased risk of haemorrhagic transformation in thrombolysed patients (OR 2.39; 95% CI 0.88-6.47), but not higher than iv thrombolysis, with a 15% absolute reduction (OR 0.55; 95% CI 0.31-1.00) of the incidence of combined *endpoint* death/dependency at 90 days.

Regarding basilar artery occlusion, associated with the highest case fatality (86%-91%), controlled studies with thrombolysis are lacking and available data come from small non-randomised studies with ia urokinase or iv rtPA (overall treated patients, 170).

Intraarterial thrombolysis, which has not yet obtained regulatory approval for stroke treatment, requires experience in stroke management and an interventional neuroradiologist. Treatment should therefore limited to clinical trials and subgroups of patients carefully selected after informed consent.

Therefore ia thrombolysis should be considered only in suitable centres able to ensure careful selection of patients and optimal procedural and post-procedural management. The ia therapeutic option is reserved mainly for hemispheric stroke patients within 6 hours of symptom onset (best between 3 and 6 hours), particularly the most severely impaired, and for basilar artery occlusion patients, without signs of infarction on CT or MRI, even over 6 hours after symptom onset.

Another condition requiring rapid identification of the presence and site of vessel lesions is acute ICA occlusion in the extracranial segment, because of the possible benefit that can be derived from the surgical approach. The literature currently does not give data from randomised trials, but only small case series; nevertheless, in our experience, a careful selection of patients guarantees a significantly better outcome for this approach.

Iv thrombolysis, currently the “standard of care” for acute stroke treatment (FDA), is far from optimal, since literature evidence demonstrates that only a small sample of stroke patients is eligible. The studies in progress involve several thrombolytic drugs or the development of new criteria for time window extension and an intraarterial or sequential approach. They are part of efforts to improve indications and appropriateness in order to achieve better outcomes.

References

1. Malferrari G, Zedde M, Marcello N. Role of ultrasound vascular imaging in the acute phase of stroke. *Vascular Disease Prevention* 2008;5:252-269
2. Malferrari G, Sanguigni S, Accorsi F. *Eco color doppler transcranico. Testo-atlante (con DVD)*. Mattioli 1885 publishers 2006
3. Saqqur M, Uchino K, Demchuk AM et al. CLOTBUST Investigators. Site of arterial occlusion identified by transcranial Doppler predicts the response to intravenous thrombolysis for stroke. *Stroke* 2007;38:948-954