A New Therapeutic Strategy for Acute Ischemic Stroke
Sequential Combined Intravenous tPA-Tenecteplase for Proximal Middle Cerebral Artery Occlusion Based on First Results in 13 Consecutive Patients

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Background and Purpose—Intravenous tissue-type plasminogen activator (IV tPA) frequently fails to recanalize proximal middle cerebral artery (MCA-M1) obstructions, preventing favorable outcomes. Only neurointerventional procedures prevail in these cases, but well-equipped centers remain scarce. A new therapeutic strategy consisting of a second IV thrombolysis with low-dose tenecteplase was applied.

Methods—Consecutive patients with an MCA-M1 occlusion that did not reopen at the end of IV tPA perfusion received IV tenecteplase (0.1 mg/kg). Partial or complete thrombolysis in myocardial infarction recanalization (Thrombolysis In Myocardial Infarction grade 2/3) and intracerebral hemorrhage were assessed by magnetic resonance imaging 24 hours later. Clinical outcomes at 3 months were evaluated with the modified Rankin score.

Results—Among 40 patients with MCA-M1 occlusions who received IV tPA, 13 were treated according to the protocol of sequential combined IV thrombolytics. Baseline National Institutes of Health Stroke Scale score was 15. At a mean of 16.8 hours after IV thrombolysis, the recanalization rate was 100% (2 with Thrombolysis In Myocardial Infarction grade 2, 11 with Thrombolysis In Myocardial Infarction grade 3). Intracerebral hemorrhage occurred in 4 of 13 (31%) patients, with no symptomatic hemorrhage. Good clinical outcomes (modified Rankin score 0/1) were achieved in 9 of 13 (69%) patients. Functional outcomes were very similar to those of 13 patients with early IV-tPA recanalization. Among 4 patients treated as protocol violations, 1 presented with a lack of recanalization and a parenchymal hematoma type 2.

Conclusions—For patients with MCA-M1 occlusions treated with IV tPA but without early recanalization, a second bolus of IV tenecteplase (0.1 mg/kg) may be a relatively safe, effective, and easy option in carefully selected cases, but additional studies are needed to confirm these findings. (Stroke. 2011;42:1644-1647.)

Key Words: middle cerebral artery occlusion stroke, acute thrombolysis tPA tenecteplase

Intravenous recombinant tissue-type plasminogen activator (IV tPA) within 4.5 hours of stroke symptom onset is currently the only US and European approved therapy for acute ischemic stroke. However, up to 50% of patients have no reported clinical benefit, mostly because of failed recanalization of the occluded artery. In conventional angiography or magnetic resonance (MRA) or computed tomography angiography trials of IV tPA, the rate of early partial or complete recanalization of occluded proximal middle cerebral arteries (MCA-M1) ranged from 25% to 50%. In clinical practice, management of MCA-M1 occlusion constitutes the main challenge for neurologists, and clinical outcomes of these patients are strongly correlated with early recanalization. Thus, a strategy sequentially combining IV tPA and an intra-arterial chemical and/or mechanical method was developed. Such rescue therapy is reportedly feasible and safe, with a higher recanalization rate and better clinical outcome than IV tPA alone. However, intra-arterial therapy has the disadvantage of prolonged time-to-treatment initiation and requires specialized angiographic techniques.

Recently, we described a patient with a basilar artery occlusion that was recanalized after a second bolus of the IV thrombolytic tenecteplase (TNK), yielding a very good clinical outcome. Herein we present the results of the first 13...
patients with MCA-M1 occlusions treated with the novel approach of sequentially combining 2 IV thrombolytics.

Methods
From May 2009 to May 2010, patients admitted to the stroke center of the Fort-de-France University Hospital (Martinique, French West Indies) with symptomatic MCA-M1 occlusions were included in this open trial. The research protocol was approved by the Ethics Committee of Fort-de-France University Hospital, and patients or their representatives (for example, a family member) gave written, informed consent.

Patients
Patients were selected on the basis of the following inclusion criteria: (1) entire therapeutic procedure performed within 6 hours of symptom onset; (2) MCA-M1 occlusion on MRA, either isolated or associated with an internal carotid artery occlusion, but T-shaped internal carotid artery or carotid-sylvian occlusions were excluded; (3) lesion volume <30% of the MCA territory on diffusion-weighted (DWI) magnetic resonance imaging (MRI) images; (4) Thrombolysis In Myocardial Infarction (TIMI) grade 0 (complete occlusion), 1, minimal contrast-medium perfusion; 2, partial flow; 3, complete flow) indicating an absence of recanalization (TIMI 0/1) on a second MRA, performed on completion of the IV-tPA infusion; (5) absence of new cerebral hemorrhage of any type on the second MRI; (6) absence of coagulopathy, with an International Normalized Ratio <1.5; and (7) no National Institutes of Health Stroke Scale (NIHSS) score cutoff, but a frank MRI diffusion-clinical mismatch was required. In addition, patients could be eligible, despite significant neurologic improvement after the IV-tPA infusion, if the control MRA showed a persistent MCA-M1 occlusion.

Procedure
Sequential Combined IV Thrombolysis Protocol
Patients with MCA-M1 occlusions were initially treated with full-dose (0.9 mg/kg) IV tPA. Arterial pressure and glycemia were monitored according to standard recommendations. After the post-IV-tPA MRI, patients who met the inclusion criteria received a IV bolus of TNK (0.1 mg/kg). They were then clinically monitored, and a third MRI was performed within the next 24 hours.

Clinical Assessment
Systematic NIHSS score evaluations were performed at admission, at the end of IV tPA, 1 hour after the IV-TNK bolus, 24 hours after admission, and at discharge. Significant neurologic improvement was defined as an NIHSS score decrease of ≥4 points, whereas a ≥4-point increase identified clinical deterioration. Early neurologic improvement was defined as a significant NIHSS score decrease 1 hour after the IV-TNK bolus. Patient recovery was assessed with the modified Rankin score (mRS) at 3 months, with mRS ≤1 defined as a good outcome.

MRI Assessment
The MRI protocol included DWI, fluid-attenuated inversion recovery, gradient-echo sequences, and time-of-flight MRA of the intracranial and extracranial arteries. Three systematic MRIs were performed: at admission, 30 minutes after the end of IV-tPA infusion, and within the next 24 hours. If the 24-hour MRI showed any bleeding, another MRI was performed at 36 to 48 hours to categorize the final type of intracerebral hemorrhage. In addition, a computed tomography scan or MRI was performed during patient follow-up in the case of clinical deterioration. Two neuroradiologists (M.A. and B.B.) determined the Alberta Stroke Program Early CT (ASPECT) score on DWI sequences and TIMI grade on MRA. Therapeutic response was evaluated as the recanalization rate according to the TIMI scale on the 24-hour MRI.

Safety assessment was based on the incidence of intracerebral hemorrhage during the first 36 hours after treatment, according to the European-Australian Cooperative Acute Stroke Study II classification. Symptomatic hemorrhage was defined as bleeding seen on the follow-up MRI with significant worsening of the NIHSS score.

Statistical Analysis
All values are expressed as mean±SD. Student’s t test, Fisher’s exact test, and Wilcoxon’s signed-rank test were used to analyze differences between subgroups of MCA-M1 occlusion patients. Significance was defined as P<0.05.

Results
During the study period, 40 patients with an MCA-M1 occlusion met IV-tPA criteria and were treated at a mean of 174±47 minutes after symptom onset. Among them, 15 (37.5%) had early recanalization (TIMI 2/3). Of the 25 patients with nonrecanalized occlusions, 12 had exclusion criteria for the sequential combined IV thrombolysis protocol: lesion volume >30% of the MCA territory on DWI-MRI (n=6), >6 hours since the first symptoms (n=4), intraventricular bleeding (n=1), and oral anticoagulant use, with an International Normalized Ratio >1.5 (n=1). Thirteen patients met the inclusion criteria for the new treatment protocol and received IV TNK. However, 4 additional patients with an isolated MCA-M1 occlusion received IV TNK as protocol violations: 2 had TIMI 2 on the immediate post-IVPA MRA, incorrectly assessed as TIMI 0; 1 had a lesion volume >30% of the MCA territory; and the last had paraneoplastic coagulopathy and was treated >10 hours after symptom onset.

The baseline characteristics of the 13 correctly included patients were as follows: mean age, 64±17 years; 8 men and 5 women; mean systolic blood pressure, 136±22 mm Hg; mean glycemia, 1.11±0.18 g/L; NIHSS scores, 15.5±5.3 at baseline and 12.4±6.9 after tPA; and ASPECTS DWI score, 8±1. Eleven had isolated MCA-M1 occlusions, and 2 had associated intracranial internal carotid artery blockage.

The clinical and neuroradiologic outcomes after the 2 stages of IV thrombolysis are reported in Table 1. After completing IV tPA, 3 patients improved dramatically but received IV TNK because their control MRI showed persistent TIMI 1 MCA-M1 occlusions. Ten patients showed no significant neurologic change or angiographic improvement (TIMI=0).

One hour after the IV-TNK bolus, 6 patients demonstrated early neurologic improvement. At 24 hours, 11 of 13 (85%) patients showed significant neurologic improvement, with a mean NIHSS score of 8.6. Control MRI, at a mean of 1002 minutes (16.8 hours) after the IV-TNK bolus, showed 100% recanalization: partial in 2 and complete in 11. Two patients had moderate neurologic deterioration at 24 to 48 hours, after having had early neurologic improvement at 1 hour. In both cases, DWI sequences revealed ischemic signal extension, without arterial reocclusion; ischemic reperfusion syndrome was therefore suspected, and their clinical outcomes were subsequently very favorable. Intracerebral hemorrhage occurred in a third of the patients, including 1 with hemorrhagic infarction type 1 and 3 with hemorrhagic infarction type 2 (Figure in the online-only Data Supplement, http://stroke.ahajournals.org). No symptomatic intracerebral hemorrhage occurred. Four patients experienced mild buccal bleeding, but no severe systemic bleeding was observed.
The 4 protocol-violation patients evolved as follows: 2 with TIMI 2 after tPA showed TIMI 3 on MRI at ∼24 hours after tNK, with hemorrhagic infarction type 2 in 1; mRS at 3 months was 2 in both. The patient with a lesion volume >30% of the MCA territory recanalized to TIMI 3 but remained severely disabled by 3 months (mRS=5). Outcome was very bad in the fourth patient with paraneoplastic coagulopathy: he remained at TIMI 0 and developed a parenchymal hematoma type 2 outside the initial infarct, and then he expired at day 7 from multiple recurrent intracerebral bleeding episodes.

**Discussion**

The first results obtained with our new therapeutic strategy for acute ischemic stroke with MCA-M1 occlusions resistant
to IV tPA (TIMI 0/1) and followed by a second IV thrombolysis with TNK (0.1 mg/kg) suggest that it can achieve a high recanalization rate and favorable outcomes. Moreover, this strategy would concern high numbers of patients with MCA-M1 occlusions eligible for IV tPA, representing a third of our clinical practice.

Our observations strongly suggest that patients selected according to our protocol criteria, mainly, a frank clinical–MRI-diffusion mismatch, whose obstructions were recanalized after sequential combined IV thrombolyzes, may have clinical outcomes as good as those of patients in whom recanalization was achieved with classic IV tPA alone, under the same safety conditions. The similar intervals from symptom onset to final treatment for these 2 groups of thrombolized patients probably played a crucial role in their similar clinical outcomes. Finally, as repeatedly reported previously, our results support the strong correlation between successful recanalization and good clinical outcomes at 90 days after IV thrombolysis.

MCA-M1 is the most frequently occluded artery among the so-called proximal arterial occlusions. Early IV-tPA–induced recanalization rates for MCA-M1 occlusions do not exceed 25% to 50%. Moreover, early recanalization is strongly associated with a final favorable clinical outcome.3 For patients with unsuccessful early IV-tPA recanalization, a second-line intra-arterial strategy is increasingly described as feasible and safe. However, such intra-arterial rescue therapy is limited by the time-to-treatment initiation and recanalization and by the need for specialized angiographic techniques that are almost exclusively available in tertiary-care centers. Hence, most hospitals involved in MCA occlusion management are not equipped for intra-arterial treatment, making IV thrombolysis the sole therapy available.

Our new strategy, proposed herein, has the considerable advantage of being feasible in the majority of hospitals managing acute stroke because of the extreme simplicity of the procedure. The decision can be based on a 1-hour post-tPA MRA, computed tomography angiography, or even an ultrasound scan to verify persistence of the MCA-M1 occlusion. Moreover, the second-line IV thrombolysis is feasible immediately, as soon as the decision is made. The safety of the combined IV-tPA–TNK procedure in our limited experience appears to be acceptable. Finally, low-dose TNK is considerably less costly than the entire neurointerventional procedure.

TNK is a genetically engineered mutant tPA. Compared with tPA, TNK has a longer half-life (20 vs 4 minutes), is 80-fold more resistant to plasminogen activator-1, and has a 14-fold higher fibrin avidity. In pilot dose-escalation studies and in a small open trial,3 the 0.1-mg/kg dose of TNK was shown to be as effective and safe as tPA for the treatment of acute ischemic stroke. We hypothesized that the sequential combination of IV tPA and IV TNK could have synergistic effects on clot lysis, leading to the very high recanalization rate of occluded MCA-M1 in our study, even though experimental data supporting this postulate are lacking. However, our small study has several serious limitations. Notably, very few subjects were included, and there was no control group. Because of the relatively high dose of IV thrombolitics, the risk of symptomatic hemorrhage needs to be specifically evaluated in future studies. As stated earlier, we lacked immediate post-TNK MRA to ascertain the specific efficacy of the second-line IV thrombolysis. tPA recanalization rates are higher at 24 hours than at 1 hour, as some later recanalization occurs during the first hours. Indeed, the success with TNK observed in our patients is likely a partial tPA success. However, only 3 of 10 patients with no early recanalization had progressed to TIMI 2 at 24 hours, compared with TIMI 2/3 for 13 of 13 patients who received the combined tPA-TNK therapy, findings strongly suggestive of more rapid TNK-induced recanalization. Finally, IV-tPA efficacy probably depends on the clot burden, and efficacy of the combined IV-tPA–TNK strategy could be limited to relatively small thrombi. The techniques for measuring the length of an intra-arterial clot have only been developed very recently and are based on computed tomography angiography or thin-slice, nonenhanced computed tomography reconstructions.6 Further investigations with these techniques should be conducted to evaluate which thrombus size is amenable to combined IV thrombolysis.

In conclusion, our results suggest that, for patients with MCA-M1 occlusions that fail to recanalize early after conventional IV tPA, the sequential combination strategy with IV TNK (0.1 mg/kg) could be a universally feasible option in carefully selected cases. Because approximately one third of patients with an MCA-M1 occlusion and who are eligible for IV thrombolysis are potential candidates, further studies are warranted to confirm these first results.

Sources of Funding
This study received funds from the French Ministry of Health (“Projets Hospitaliers de Recherche Clinique Régionaux”).

Disclosures
None.

References
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Stroke. 2011;42:1644-1647; originally published online April 28, 2011; doi: 10.1161/STROKEAHA.110.610147

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0039-2499. Online ISSN: 1524-4628

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http://stroke.ahajournals.org/content/42/6/1644

Data Supplement (unedited) at:
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SUPPLEMENTAL MATERIAL
Figure. The four cases of hemorrhagic infarctions type 1 (A) and type 2 (B, C and D) (post-TNK MRI, T2* echo sequence)