Desmoteplase Extends Stroke Treatment Window

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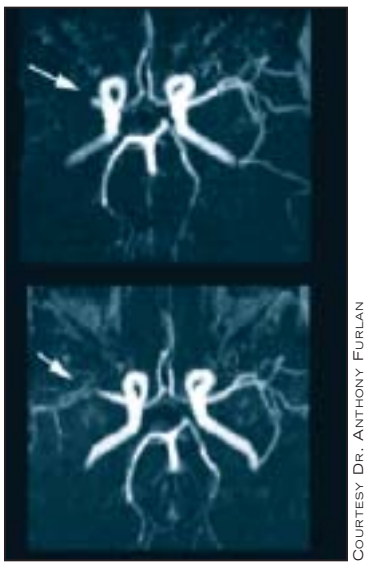
BALTIMORE — The investigational drug desmoteplase combined with imaging to identify appropriate patients could push the treatment opening beyond 3 hours for some patients with acute ischemic stroke, according to Dr. Anthony Furlan, section head of stroke and neurologic intensive care at Cleveland Clinic.

"Even though intravenous tissue plasminogen activator has been an enormous breakthrough in stroke therapy, 95% of patients don't get treated with it," Dr. Furlan said at the annual neurocritical care and stroke conference sponsored by Cleveland Clinic. "[W]e're not going to be treating lots of patients if we're confined to a 3-hour drug. An estimated 80% of stroke patients don't get to the hospital within the first 3 hours after onset."



Courtesy Dr. Anthony Furlan

Right middle cerebral artery occlusion is on baseline magnetic resonance angiogram (top): the defect resolved 28 hours after IV desmoteplase (bottom).

Animal trials have shown that desmoteplase—a plasminogen activator derived from vampire bat saliva—may be a better treatment option for acute stroke than is tissue plasminogen activator (TPA) for several reasons. Desmoteplase is not neurotoxic, and it does not activate β-amyloid, unlike TPA. In addition, desmoteplase has a long half-life, which allows for bolus injection. "That's useful for dosing control," said Dr. Furlan. In animal models, desmoteplase also has been associated with fewer hemorrhages than has TPA.

The Desmoteplase in Acute Ischemic Stroke (DIAS) and the Dose Escalation Study of Desmoteplase in Acute Ischemic Stroke (DEDAS) trials were the first acute stroke thrombolytic trials to select patients for treatment after 3 hours based on perfusion imaging. Dr. Furlan was the principal investigator for the DEDAS trial. Desmoteplase is being jointly developed by Forest Laboratories Inc. and Paion AG.

Enrollment in the DIAS and DEDAS trials was limited to patients who had stroke onset within 3-8 hours and had a 20% perfusion-diffusion mismatch on baseline MRI. Reperfusion was defined as a 30% or better improvement in mean transit time on perfusion MRI or an improvement of two thrombolysis in myocardial infarction (TIMI) flow grades.

In an unpublished pooled analysis of both trials, none of the 35 patients who received placebo or the 30 patients who received 125 mcg/kg desmoteplase (as bolus) had symptomatic intracranial hemorrhage. Only 1 of the 29 patients (3.4%) who received 90 mcg/kg desmoteplase (as bolus) had symptomatic intracranial hemorrhage.

Mortality was 5.7% for the placebo group, 6.9% for the 90 mcg/kg desmoteplase group, and 3.3% for the 125 mcg/kg desmoteplase group. In addition, perfusion at 4-8 hours (based on MRI) was closely linked with clinical outcome at 90 days, with patients in the 125 mcg/kg group having the best results.

Based on a Rankin scale shift analysis of pooled data from the two trials, "at the 125-mcg dose—with a very small number of patients—we had a statistically significant clinical benefit, defined by improvement in Barthel [index], modified Rankin [scale], and NIH [stroke scale]," said Dr. Furlan.

For the 125-mcg dose, at 3 months there was a "statistically significant Rankin shift, meaning that we saw a positive benefit across the whole spectrum of the modified Rankin scale," said Dr. Furlan.

"Is the drug alone sufficient? Well, my thinking is no. We have to combine the drug with proper patient selection," he said. Imaging appears to be key to identifying patients who will benefit.

In the Diffusion-Weighted Imaging/Perfusion-Weighted Imaging Evaluation for Understanding Stroke Evolution (DEFUSE) pilot study, researchers attempted to determine if baseline MR images can identify stroke patients who have a good clinical response when treated 3-6 hours after symptom onset.

MRI was performed before and 3-6 hours after treatment with intravenous TPA, administered 3-6 hours after symptom onset. Baseline MRI profiles were used to categorize patients into subgroups, and clinical responses were compared based on whether early reperfusion was achieved.

The researchers identified a specific type of mismatch—malignant mismatch—that was associated with severe intracranial hemorrhage and poor outcome after reperfusion. Malignant mismatch was defined as a defusion lesion greater than 100 cc in volume and/or a perfusion lesion greater than 100 cc in volume.

For patients with target mismatches—all mismatches other than malignant mismatches—with early reperfusion, there was an almost statistically significant clinical benefit, compared with all other mismatch patients. In addition, those with target mismatch and early reperfusion were more likely to achieve a favorable clinical response than were those with target mismatch but no early reperfusion (Ann. Neurol. 2006;60:508-17).

Dr. Furlan disclosed that his research has been supported by Forest Laboratories, Paion, and Abbott and that he has received speaking honoraria from Bristol-Myers Squibb/Sanofi and Genentech. ■