

MRI Opens Thrombolysis Window After Stroke

BY MITCHEL L. ZOLER
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NEW ORLEANS — The presence of a favorable pattern of cerebral perfusion on magnetic resonance imaging may tell physicians which patients with acute ischemic stroke stand to benefit from thrombolysis even hours after the onset of symptoms.

Findings from two phase II studies using MRI show that some patients were able to safely receive a thrombolytic drug as long as 9 hours after the onset of their stroke symptoms. Results from the most recent of these studies were reported at the 30th International Stroke Conference.

Results from the prior study, which was conducted in Europe, were published in January.

"These are the first trials to test the hypothesis that selecting patients with favorable imaging patterns can extend treatment beyond the current 3-hour window," said Anthony J. Furlan, M.D., head of the section of stroke and neurologic intensive care at the Cleveland Clinic and principal investigator of the new study.

"If this hypothesis is borne out, it could have an enormous impact on how we use thrombolytic therapy for stroke," he added. "It has the potential to at least triple the number of acute stroke patients who are eligible for thrombolytic therapy."

Like the study done in Europe, Dr. Furlan's research used a combination of perfusion-weighted and diffusion-weighted imaging by MR to identify patients with at least a 20% mismatch between the two.

The mismatch is a marker for patients with a significant penumbra region in their brain, tissue that might be salvageable by thrombolytic therapy because it is still viable despite being hypoperfused. "Most patients who made it to MR were eligible," Dr. Furlan said. "The MR criteria did not exclude a lot of patients."

The other novel feature of both the European and U.S. studies was the thrombolytic drug used: desmoteplase, a plasminogen activator derived from vampire bat saliva. Desmoteplase has several potential advantages over tissue plasminogen activator (TPA).

In animal studies, desmoteplase showed no neurotoxicity, and it did not activate β -amyloid, a process that's been linked to an increased risk of intracranial hemor-

rhage. Desmoteplase also has very high specificity and selectivity for fibrin and a long serum half-life of 4 hours. This last property means that it can be given as a bolus dose and may also help prevent acute reocclusion of newly opened arteries.

Desmoteplase is being developed in the United States by Forest Laboratories and in Europe by PAION, a German drug company. Dr. Furlan is a consultant to both companies, and he received compensation from both for acting as a principal investigator in these and ongoing studies.

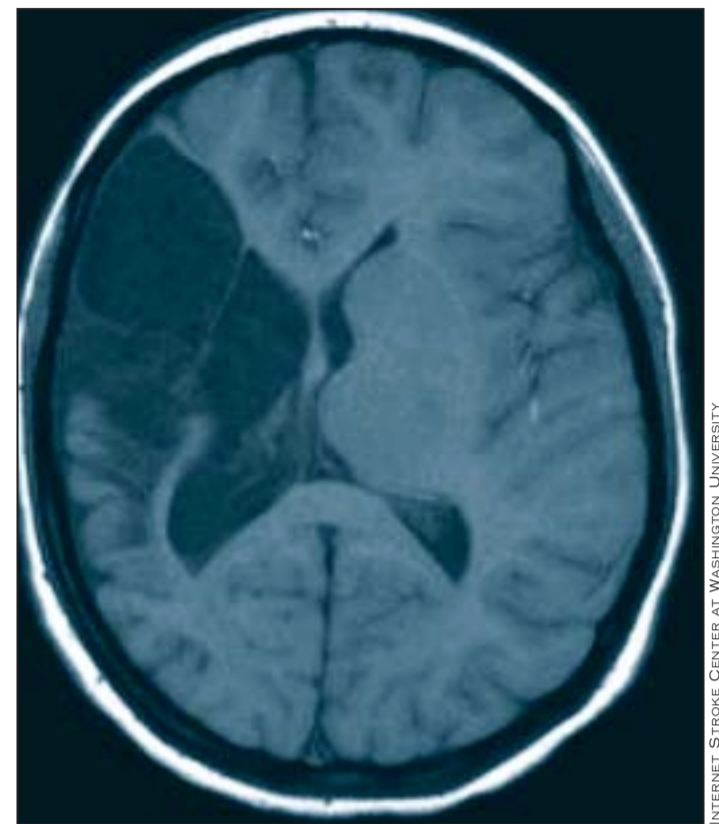
The U.S. study involved enrollment of 37 patients who all met the entry MR criteria. After randomization, 14 of the patients were treated with 90 mcg/kg desmoteplase, 15 received 125 mcg/kg desmoteplase, and 8 received placebo. The average time to treatment was 7 hours. Although patients could enter treatment as long as 9 hours after the onset of their stroke symptoms, the top reason for excluding patients from the study was that they had gone beyond the 9-hour window.

The U.S. study's primary end point was the rate of symptomatic, intracranial hemorrhage (sICH), which occurred in none of the patients. In the prior European study, one sICH occurred among 15 patients treated with 90 mcg/kg and none among 15 patients treated with 125 mcg/kg. Thus, the overall rate of sICH in these two studies at these two doses was one among 59 treated patients, a 1.7% rate that was lower than the 6% rate with TPA in routine practice, noted Dr. Furlan at the conference, sponsored by the American Stroke Association.

In the European study, 30 patients received substantially higher doses of desmoteplase, and they had a 27% rate of sICH. In this higher-dose group, the lowest desmoteplase dose associated with intracranial hemorrhage was 294 mcg/kg.

The new study was not powered to show significant differences in clinical outcomes.

The reperfusion rate was 38% in the control group, 18% among those who received 90 mcg/kg, and 53% among those who received 125 mcg/kg. Improved clinical outcomes at 90 days were seen in 25% of those in the placebo group, 29% of those in the low-dose arm,



In this T1-weighted MRI, a large infarct is clearly visible in the middle cerebral artery of an 18-year-old woman.

and 60% of those in the high-dose arm. There was no reduction of safety or efficacy in the patients treated 6-9 hours after their stroke onset, compared with those treated 3-6 hours after onset, Dr. Furlan reported.

The results were promising enough for a phase III study to start this spring, retesting both desmoteplase doses against placebo in a total of 186 patients, Dr. Furlan said. The next study will also test perfusion CT imaging as well as MR imaging because some centers have easier access to CT scanners.

If study results continue to document the safety and efficacy of desmoteplase paired with imaging to identify appropriate patients, eventually desmoteplase will have to be compared with TPA in a head-to-head study, he said. ■

Genetic Variant Increases Risk of Late-Onset Alzheimer's

BY SUSAN
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Contributing Writer

Strategies for the prevention and treatment of late-onset Alzheimer's disease may be improved by the identification of a gene variant that seems to increase Alzheimer's disease, according to a report by Lars Bertram, M.D., of MassGeneral Institute for Neurodegenerative Diseases, Charlestown, Mass., and his associates.

Variants in the ubiquitin 1 (*UBQLN1*) gene, located on chromosome 9, may substantially increase the risk of late-onset Alzheimer's disease, which accounts for over 90% of the disease, other investigators have reported.

Dr. Bertram and his associates examined two groups of patients; the first consisted of 1,439 subjects from 437 families with Alzheimer's disease who participated in the National Institute of Mental Health multiplex family study between 1991 and 1997. Of that group, 994 patients had Alzheimer's, 411 were unaffected, and 34 had unknown phenotypes.

The mean age at disease onset was 72 years, the investigators said (*N. Engl. J. Med.* 2005;352:884-94).

Evaluation of 19 single-nucleotide polymorphisms in three genes within the chromosome 9q linkage region showed that Alzheimer's disease was significantly associated with two single-nucleotide polymorphisms in *UBQLN1* and one in *APBA1*.

Haplotype block structure estimates showed that the single haplotype (H3), almost exclusively defined by the risk allele of UBQ-8i, was associated with a significantly increased rate of transmission to affected subjects. The testing of *APBA1* polymorphisms did not indicate such transmission.

Ubiquitin 1 encodes the protein ubiquitin 1, regulates protein degradation, interacts with presenilin 1 and presenilin 2, and promotes the accumulation of presenilin in vitro, they said.

Findings from the second investigation, the Consortium on Alzheimer's Genetics study, showed that the rate of transmission of the H3 haplotype was increased among subjects with Alzheimer's disease. Investigators found no association with rs1411483 in *APBA1*.

Specimen collection began in 1999 and has been completed for 224 Alzheimer's patients and 265 unaffected siblings. Affected participants were at least 50 years old at disease onset; mean age at onset was 71 years.

Analyses by Dr. Bertram and colleagues on data merged from the two family groups showed the most pronounced single-local signals for UBQ-8i followed by rs2781002 and rs2780995.

Dr. Bertram's group also studied RNA extracts from neocortical brain tissue samples to see if the risk allele UBQ-8i affects the splicing of exon 8 in the *UBQLN1* mes-

Most genetic analyses of Alzheimer's have been done on groups too small to demonstrate moderate genetic effects like that of *UBQLN1*.

sage. They found a relationship between the UBQ-8i allele and a *UBQLN1* transcript lacking exon 8 in the 25 samples from patients with Alzheimer's disease.

In an accompanying editorial, Thomas D. Bird, M.D., called *UBQLN1* "intriguing as a candidate gene because of its potential role in the proteasome degradation of proteins and its interaction with *PS1* and *PS2*."

"As always, this new association requires replication and confirmation in additional populations," commented Dr. Bird, who is professor of neurology, medicine, and psychiatry at the University of Washington, Seattle, and a research neurologist at the Veterans Affairs Medical Center in Seattle (*N. Engl. J. Med.* 2005;352:862-4).

Dr. Bertram's group observed that "the rampant inconsistencies encountered in genetic analyses of putative candidate genes for Alzheimer's disease in the literature to date" may stem from the fact that most studies are done on groups too small to show moderate genetic effects like that of *UBQLN1*, instead of the more pronounced effects of *APOE*. ■