Penumbral Imaging Propels Trials Toward Wider Therapeutic Window

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More than a decade after the last FDA approval for a stroke drug, vampire bat saliva navigates process using updated techniques

It's been a long, frustrating 12 years since an acute stroke drug last won over the FDA, a time in which the percentage of eligible patients actually helped by the drug has remained stuck in the single digits. All signs indicate, however, that the next acute stroke therapy to win approval will do so on the strength of a very different type of clinical trial, one that uses advanced imaging techniques to demonstrate the potential for doubling or even tripling the number of patients who may benefit.

Using penumbral imaging to identify salvageable regions of brain, new clinical trials are demonstrating that thrombolytic therapies can be effective well beyond the 3-hour window established with the 1996 approval of recombinant tissue plasminogen activator. Research even suggests that tPA itself can be effective up to 6 hours from stroke symptom onset in patients with an identifiable penumbra.

"Imaging could allow for a huge extension of the time window or even eliminate the time window," said Chelsea S. Kidwell, MD, an associate professor of neurology at Georgetown University and medical director of the Georgetown and Washington Hospital Center stroke centers.

Time is still brain. The sooner a stroke patient receives treatment—no matter what type of treatment—the better the odds it will be effective. Many clinicians feel, however, that the 3-hour time limit is the primary reason why as few as 3% of all stroke patients receive tPA. With ongoing trials suggesting that window could be extended to 9 hours, if not longer, many more patients stand to benefit.

"We will never treat more than 10% of patients if we're always constrained to 3 hours," said Anthony J. Furlan, MD, director of the Vascular Neurology Program and associate director of the Cerebrovascular Center at The Cleveland Clinic.

He estimated that an additional 10% to 15% of patients could receive therapy for every 3 hours added to the treatment window.

SELECT COMPANY

Expanding the time window alone does not appear to be enough, however. Several multicenter randomized placebo-controlled trials1-4 have tested the effectiveness of intravenous tPA beyond 3 hours using the same eligibility criteria as the pivotal 1995 clinical trial on which the drug's approval was based5 and failed to demonstrate efficacy. A pooled analysis of the same trials did suggest a benefit beyond 3 hours, but not extending to 6 hours.6

In a paper published in March 2006, however,7 German researchers studied 174 stroke patients who were selected for intravenous tPA treatment up to 6 hours from symptom onset. Patient selection was based on the presence of an ischemic penumbra, or mismatch, shown on MR diffusion- and perfusion-weighted imaging (DWI-PWI), meaning the MR perfusion volume of their brains delineating treatable stroke damage was at least 20% larger than the volume's diffusion core correlating with dead or irretrievably damaged tissue.

They then compared the results with those of the pooled treatment (n = 1085 patients) and placebo (n = 1081 patients) groups from the earlier analysis. Patients in the MRI-treated group were more likely than patients in either pooled group to have favorable 90-day outcomes based on the modified Rankin Scale (mRS), and they were significantly less likely than those in the pooled treatment group to have experienced symptomatic intracranial hemorrhage (sICH).

Even more convincing than the German retrospective assessment were the findings from the Diffusion-weighted imaging Evaluation For Understanding Stroke Evolution (DEFUSE) prospective...
multicenter study published 6 months later.8 DWI-PWI was not used for selection but was performed on 74 consecutive stroke patients given tPA within 3 to 6 hours of symptom onset. The presence or absence of early reperfusion, assessed using PWI immediately following therapy in 45 patients, was not associated with 30-day clinical outcome, measured using the National Institutes of Health Stroke Scale (NIHSS) and the mRS, in the overall group; however, those with early reperfusion and DWI-PWI mismatch were significantly more likely to have a favorable clinical response than patients with a DWI-PWI mismatch without early reperfusion (56% versus 19%). By comparison, none of the 4 patients with early reperfusion and no mismatch had favorable clinical outcomes.

The DEFUSE findings also suggest that not all mismatches are created equal. Of those patients with mismatch and early reperfusion, a pattern of large DWI lesions and/or large PWI lesions with long delays on a Tmax perfusion map was seen in 3 patients who died following sICH. When the patients with this "malignant mismatch" profile were excluded from the mismatch/early reperfusion analysis, the rate of favorable clinical response in the remaining "target mismatch" patients improved from 56% to 67%.

"The DEFUSE study seems to support what most of us thought, which is that you can extend the tPA window if you have the appropriate mismatch," said Marc Fisher, MD, a professor of neurology at the University of Massachusetts Medical School.

For further confirmation, clinicians and researchers are looking to the results of the Echoplanar Imaging Thrombolysis Evaluation Trial (EPITHET) conducted at 14 centers in Australia, New Zealand, and Europe.9 The study had enrolled 101 patients as of February. All had undergone DWI-PWI before being randomly selected to receive either intravenous tPA or a placebo 3 to 6 hours after symptom onset. Researchers hope to show that tPA in patients with DWI-PWI mismatch is associated with lower rates of DWI lesion expansion (from baseline to 90 days) and increased reperfusion. The study was completed in June.

DESMOTECPLASE DISAPPOINTS

Meanwhile, the most highly anticipated stroke imaging trial of the year left radiologists scratching their heads about the disappointing results. No more than 47% of acute stroke patients administered the clot-dissolving protein desmoteplase 3 to 9 hours after the onset of symptoms showed improvement. The positive outcome rate was about the same among patients given a placebo. Desmoteplase (desmodus rodundus salivary plasminogen activator) is a thrombolytic agent derived from vampire bat saliva that many expect to be the next stroke drug to win FDA approval. It has been granted fast-track status. Potential advantages of desmoteplase include a longer half-life than tPA, which allows it to be administered in a single bolus injection rather than a continuous drip, and a high specificity for fibrin, which theoretically lowers the associated risk of hemorrhage. Clinical trials of desmoteplase from phase II onward have specified DWI-PWI mismatch as an inclusion criterion. Researchers used functional MRI or perfusion CT in the Desmoteplase In Acute Ischemic Stroke study (DIAS II) to identify candidates for treatment. Promising candidates exhibited a positive diffusion-perfusion mismatch. CT perfusion used different parameters to generate the same results. In total, 186 patients received either placebo or 1 or 2 doses of desmoteplase within 3 to 9 hours of symptom onset.

Compared with placebo, the clot-dissolving protein desmoteplase did not change clinical outcomes for acute ischemic stroke patients in the phase III clinical trial. Results were presented at the European Stroke Conference on May 31 in Glasgow by Dr. Werner Hacke, director of neurology at the University of Heidelberg in Germany.

Early desmoteplase studies suggested that the tPA treatment window could be expanded, particularly in patients with perfusion-diffusion mismatch. In the current study, however, clinical outcome did not differ among the 3 groups.

"This study should not be misinterpreted as proving that desmoteplase after 3 hours does not work or that patient selection after 3 hours with mismatch imaging is not reliable," said Dr. Anthony Furlan, coprincipal investigator and section head of stroke and neurologic intensive care at The Cleveland Clinic. "Rather, this study further emphasizes the complexity of treating acute stroke after 3 hours and the need for larger, more sophisticated clinical trials, the design of which will be informed by the results of trials like this one and other acute imaging-based studies."

Intravenous desmoteplase treatment appears safe, but clinical benefits remain uncertain, according to Furlan.

"We were disappointed in the results but not entirely surprised, since we were trying to answer many new questions with a small sample size," he said. "The hope was that by using new imaging technology to select patients for treatment, we could optimize patient selection. However, DIAS II
indicates that the problem of reperfusion therapy after 3 hours is more complex than we anticipated."

Furlan suggests that a study with at least 600 participants would yield more information.

RETRIEVE AND RESCUE

Researchers also are investigating whether MRI can help improve outcomes associated with the second acute stroke therapy to receive FDA approval, the Merci Retriever (Concentric Medical), a mechanical embolectomy device. Previous trials of the device12,13 demonstrated its effectiveness when used within 8 hours of symptom onset in patients with severe stroke (NIHSS score of 8 or more) who were either ineligible for tPA or in whom tPA did not achieve recanalization. The pooled results of those trials were presented in February at the annual International Stroke Conference in San Francisco.

The latest assessment of the Merci Retriever device, the MR and Recanalization of Stroke Clots Using Embolectomy (MR-RESCUE) study,14 will differ from previous trials in several ways. The most obvious, as the acronym suggests, is that one of the study's objectives is to use MRI to identify which patients will benefit from mechanical embolectomy. All 120 patients slated to be enrolled in the study will undergo MR-based penumbral imaging. After outcomes have been determined, researchers will analyze whether imaging patterns were predictive of success or failure.

In this case, however, ischemic penumbra is not being defined by DWI-PWI mismatch. Cognizant of the limitations of mismatch-based penumbral estimates, the MR-RESCUE researchers instead are using computer software modeled on quantitative diffusion and perfusion data from patients in whom recanalization was previously successful to more precisely quantify the extent of potentially salvageable tissue (Figure 1).

"We've set up all the sites so there's a computer attached to the scanner that calculates penumbra within minutes of the scan," said Kidwell, principal investigator for the study. "If we can demonstrate that this is useful, it's simply a matter of connecting a computer to the scanner, or it may be that a lot of imaging scanners can process this type of algorithm into their scanning protocols."

As in the earlier trials, outcome measures will include angiographically verified recanalization and 90-day clinical outcomes based on mRS score. MR-RESCUE patients will also undergo follow-up MRI at 7 days to confirm reperfusion, something not addressed by previous investigations. The MR-RESCUE trial will randomly select patients to receive either mechanical embolectomy or standard medical treatment, in an effort to address a common criticism of the earlier trials, in which all enrolled patients received treatment with the Merci Retriever.

"While we believe and hope the device works, it's imperative to have a control arm so that we can be sure," Kidwell said. "Probably, this will be the first and only randomized trial of mechanical embolectomy."

MIX AND MATCH

Because of the heterogeneous nature of stroke, many experts believe that the future of stroke therapy will depend not on any single form of treatment but rather some combination. DWI-PWI is being used for patient selection in a phase II trial of one such combination of the platelet aggregation inhibitor abciximab (ReoPro) and the recombinant plasminogen activator reteplase (Retavase). Inclusion criteria for the Reperfusion of Stroke Safety Study-Imaging Evaluation (ROSIE) trial include evidence of a perfusion defect on PWI and DWI lesions involving no more than one third of the middle cerebral artery territory, along with an NIHSS score of 16 or less and a time from symptom onset of 3 to 24 hours. Follow-up MRI is performed at 24 hours from the start of treatment to assess reperfusion.

Preliminary results in the first 34 patients, presented at the 2006 International Stroke Conference in Kissimmee, FL,15 suggest that acceptable reperfusion rates could be achieved with abciximab in combination with any of the tested doses of reteplase but not with abciximab alone. The study, which is scheduled to enroll 72 patients, is ongoing.

Imaging is playing a different role in another ongoing combination therapy trial, the third installment of the Interventional Management of Stroke studies, which is investigating the combined effects of intravenous and intra-arterial thrombolysis. All 900 projected enrollees in the IMS III trial will receive intravenous tPA. Those with angiographically detected occlusions will then receive 1 of 3 intra-arterial therapies: mechanical embolectomy using the Merci Retriever, conventional intra-arterial tPA, or sonothrombolysis, in which low-energy ultrasound is used along with tPA to accelerate clot lysis.

In the IMS II trial, sonothrombolysis delivered using the Neurowave microinfusion catheter (Ekos)
achieved recanalization in 69% of 30 patients, compared with 50.5% of 18 patients given intra-arterial tPA using a standard microcatheter. Those results were also presented at the 2006 International Stroke Conference.16

DAYS GONE BY

One obvious question raised by the concept of using penumbral imaging to expand the therapeutic window is just how far the window can open. Research from Johns Hopkins University School of Medicine suggests the cutoff need not be 8 hours, or even 24 hours. After recognizing that a small but not insignificant number of stroke patients who arrived as transfers from other hospitals days after symptom onset still demonstrated persistent DWI-PWI mismatch, the Johns Hopkins researchers have had success treating these patients with induced hypertension.

In a study of 42 patients in whom MRI was performed more than 48 hours after symptom onset,17 15 patients had a mismatch pattern. Nine of the 42 patients (6 with mismatch) were treated with induced hypertension, with 8 demonstrating early improvement in neurological deficits. All 6 patients with mismatch improved, and follow-up PWI confirmed reperfusion in those patients (Figure 2).

Because clinicians and researchers are not routinely looking for mismatch in patients more than 48 hours after symptom onset, it's difficult to say how many patients may fall into this category or what the best form of treatment might be, said Robert J. Wityk, MD, an associate professor of neurology and medicine and codirector of the Cerebrovascular Division at Johns Hopkins. "The disbelievers would say, here it is 3 to 4 days out and they're still seeing mismatch; it can't possibly mean anything," Wityk said. "We just want to know if there's something we can do to make them better."

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REFERENCES

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