In 1996, when the US Food and Drug Administration (FDA) approved the use of intravenous tissue plasminogen activator (IV tPA) to treat acute ischemic stroke (AIS), the rules for treatment were clear. Most centers rigorously adopted the inclusion and exclusion criteria developed for the National Institutes of Neurological Disorders and Stroke (NINDS) tPA stroke study, which included strict time limits and parameters for patient selection.1 During the intervening 14 years, strong evidence supporting the efficacy of IV tPA for acute stroke treatment has emerged, but much of the clarity about time windows and patient selection has been clouded. The rapid evolution of intra-arterial (IA) treatment options and advanced imaging has made the discussion even more complex and interesting.

**IV Thrombolysis**

The NINDS stroke trial showed that patients who received IV tPA were 30% more likely to have a favorable outcome at 90 days than those who received a placebo, which represents an absolute benefit of 11% to 13%.1 These results have become very durable, as other trials and broader clinical experience have validated these findings.

The pooled analysis of the NINDS, ECASS I and II (European Cooperative Acute Stroke Studies), and ATLANTIS A and B (Alteplase Thrombolysis for Acute Noninterventional Therapy in Ischemic Stroke) studies confirmed the NINDS results and showed that the earlier the drug was administered, the more likely a favorable outcome would result (Figure 1).2 The benefit of IV tPA out to 4.5 hours in this pooled analysis was confirmed by the ECASS III study, which, in addition to using the NINDS criteria, added age > 80, history of diabetes and stroke, National Institutes of Health Stroke Scale (NIHSS) score > 25, and anyone on warfarin regardless of the international normalized ratio to the list of exclusions.3 These data have resulted in a new guideline from the American Stroke Association stating that “in addition to patients presenting within the 3-hour window who should be treated as recommended in the 2007 guidelines, IV tPA should now also be administered to eligible patients during the time period of 3 to 4.5 hours.”4 Despite the fact that the FDA has not given its approval, stroke centers across the country are adopting the longer window in selected cases.

Desmoteplase, a plasminogen activator derived from bat saliva, showed early promise in the DIAS (Desmoteplase in Acute Ischemic Stroke) and DEDAS (Dose Escalation of Desmoteplase for Acute Ischemic Stroke) studies, which selected patients based on magnetic resonance imaging (MRI) perfusion/diffusion mismatch up to 9 hours after symptom onset.5,6 However, the pivotal phase III trial (DIAS-2) did not confirm the benefit over placebo.7

It is encouraging that real-world experience using IV tPA, as reported in the STARS (Standard Treatment With Alteplase to Reverse Stroke) study from 57 medical centers in the United States,8 the CASES (Canadian Activase for Stroke Effectiveness Study) trial from 60 centers in Canada,9 and the SITS-MOST (Safe Implementation of Thrombolysis in Stroke Monitoring Study) trial from 285 centers in Europe10 all reported the same or better safety and efficacy that has been seen in the controlled trials. The cumulative data have made it clear that IV tPA is an effective treatment for AIS. However, the challenge of transporting more people to the right hospitals within a short time window remains.

**IA Thrombolysis**

There are types of strokes in which IV thrombolysis has limited effectiveness. The recanalization rates of IV tPA for proximal large-vessel occlusion (LVO) range from 10% for the internal carotid artery to 30% for the proximal middle cerebral artery (MCA).11 These, along with carotid T and basilar artery occlusions, are strokes that carry a...
very poor prognosis if they are not revascularized. The potential advantage of IA thrombolysis (IAT) is that the drug can be delivered in high concentrations directly at the site of the clot. Many stroke centers use tPA in this fashion, but it is not approved by the FDA and, therefore, is off label. The PROACT II (Prolyse for Acute Cerebral Thromboembolism II) study was a landmark trial looking at the safety and efficacy of IA recombinant prourokinase (pro-UK) in MCA occlusions. There was an increased rate of recanalization with pro-UK versus placebo (66% vs 18%), which correlated with favorable clinical outcomes as measured by the modified Rankin scale of 0 to 2 at 90 days (40% vs 25%). There was no difference in mortality rates in the two groups. Despite this clear advantage, the drug was not approved by the FDA, and pro-UK is not available for clinical use.

The MELT (Middle Cerebral Artery Embolism Local Fibrinolytic Intervention) trial tested urokinase for MCA occlusions up to 6 hours after the onset of symptoms. The trial, which was conducted in Japan, was not completed because of the approval of IV tPA there. However, in the 114 patients who were enrolled, the recanalization rate with IA urokinase was 73.7%, with a trend toward favorable clinical outcomes.

**COMBINED IV AND IAT**

Ideally, eligible patients should have IV tPA initiated as soon as possible and then be evaluated for additional IA treatment if needed. This is often played out in the “drip-and-ship” scenario, in which the hospital where the patient first presents gives IV tPA in consultation with a comprehensive stroke center, and then the patient is transported. The combination of IV thrombolysis and IA treatment has been the subject of the IMS (Interventional Management of Stroke) trials. IMS I, combining low-dose IV tPA (0.6 mg/kg) and IA tPA, showed similar safety and efficacy outcomes to the treatment arm of the NINDS tPA trial. IMS II added the Ekos Micro-Infusion catheter (Ekos Corporation, Bothell, WA) to the protocol. It is postulated that the Ekos device increases the surface area available to the tPA, which may result in higher recanalization rates. There was a trend toward better clinical outcomes than in the NINDS trials. All of this has led to the ongoing IMS III trial, which is powered to answer the question of whether combining IV tPA with IA treatment in patients with a baseline NIHSS > 10 is more effective than IV tPA alone. If the trial is positive, it is hoped that the FDA will approve tPA for IA administration.

Also in progress is a phase III trial studying whether combining external ultrasound using transcranial Doppler technology with IV tPA in MCA occlusions is more effective than tPA alone. The phase II CLOTBUST (Combined Lysis of Thrombus in Brain Ischemia Using Transcranial Ultrasound and Systemic tPA) trial showed promising results for this approach.

**MECHANICAL EMBOLECTOMY**

The Merci Retriever (Concentric Medical, Inc., Mountain View, CA) (Figure 2), which was studied in the single-arm, multicenter MERCI (Mechanical Embolus Removal in Cerebral Ischemia) and MultiMERCI trials, was approved for clot removal in the brain by the FDA in 2004. Both trials enrolled patients up to 8 hours after symptom onset with NIHSS scores of ≤ 8. The MultiMERCI trial introduced a new version of the device and also allowed patients who had received IV tPA to be enrolled. In the MultiMERCI trial, the recanalization rate was 55% with the device alone and increased to 68% with adjunctive therapy (usually IA
tPA). The symptomatic hemorrhage rate was 9.8%, and overall, the mortality rate was 34% (25% in the recanalized group and 52% in the nonrecanalized group). Treatment with IV tPA did not increase the rate of hemorrhage. Favorable outcomes (modified Rankin scale $\leq 2$) were seen in 36% of all cases (49% of the recanalized group and 9.6% in the nonrecanalized group). A subsequent pooled analysis of both of the trials found that recanalization was the strongest predictor of a favorable clinical outcome.\textsuperscript{16}

There are now multiple versions of the Merci device. Real-world clinical experience has been collected in a registry that just finished enrollment with 1,000 patients from 36 sites. An interim analysis of 625 cases was presented at the International Stroke Conference in February 2010 by Dr. Tudor Jovin. Recanalization occurred in 77% of cases, and favorable outcomes were observed in 32.4%; the mortality rate was 34.6%. Predictors of favorable outcomes were lower baseline NIHSS scores, younger age, revascularization, and no intubation during the procedure. The paper reporting the results of the 1,000-patient registry is currently in press.

Figure 2. The Merci L5 Retriever.

The Penumbra stroke system (Figure 3) is another embolectomy device that was approved for clot retrieval by the FDA in 2007 based on an initial feasibility pilot trial and a larger, single-arm, prospective trial in 24 centers in the United States and Europe. Complete or partial revascularization occurred in 81.6% of the primary targeted vessels, with 25% favorable clinical outcomes at 90 days and 32.8% mortality.\textsuperscript{18}

Figure 3. The Penumbra stroke system (Penumbra, Inc., Alameda, CA).

Figure 4 summarizes the recanalization rates and favorable outcomes in the major IA trials. Although recanalization rates are improving, favorable clinical outcomes are not keeping pace. Going forward, it will be important to focus on ways to improve outcomes, either by more careful case selection or improvements in the procedure itself, such as only intubating patients in whom the airway is compromised, and therefore, shortening the time it takes to open the artery. Several new devices are in development, and it is hoped that these devices will make it faster and easier to achieve revascularization.

**ADVANCED IMAGING**

It is likely that a significant number of people have a large amount of salvageable tissue at the time of stroke symptom onset. Both MRI and computed tomographic (CT) technology can be used to evaluate the size of the penumbra (tissue with potential for recovery) versus the core of the stroke that is likely not to recover even with revascularization. MR perfusion-weighted imaging (PWI) defines the penumbra, and diffusion-weighted imaging (DWI) defines the stroke core. When the PWI defect is much larger than the DWI defect, it is a so-called mismatch pattern (Figure 5) and implies aggressive revascularization may be of significant benefit. When the two are of similar size, it is called a match (Figure 6), and
Revascularization is not likely to result in an improved outcome. CT perfusion mapping can provide similar information on which to base a treatment decision. In addition, CT or MR angiography can often show the site of an LVO, thereby directing the neurointerventional procedure.

The DEFUSE I (Diffusion-Weighted Imaging Evaluation for Understanding Stroke Evolution) study was designed to identify MRI patterns that are predictive of the clinical response to IV tPA administration between 3 and 6 hours after stroke onset based on pretreatment MRI profiles. In the 41% of the cases in which a mismatch pattern was observed, the clinical response to reperfusion was favorable. In the cases in which there was no mismatch, there was either no clinical benefit, or even worse, a symptomatic intracerebral hemorrhage. DEFUSE II is an ongoing trial looking at the pre-IA treatment MRI patterns and correlating them with clinical outcomes.

It is hoped that these advanced imaging techniques will lead us away from strict time windows to a more physiologic imaging evaluation of each case to determine who should be treated. The DAWN (DWI/PWI CTP Assessment in the Triage of Wake-Up and Late Presenting Strokes Undergoing Neurointervention) trial will evaluate whether perfusion imaging patterns (either MRI or CT perfusion) in strokes from 7 to 23 hours after onset can predict clinical outcomes of mechanical embolectomy. Preliminary, retrospective pilot data were presented at the International Stroke Conference in February 2010, and the conclusion was that endovascular recanalization therapies can be used with acceptable safety beyond 8 hours from witnessed or unwitnessed onset when selection is based on a mismatch pattern.

CHALLENGES AHEAD

The future looks very bright for improving outcomes for patients with AIS, with more choices of drugs and devices, as well as expanded time windows based on imaging. However, there is the continued challenge of getting people to the right place at the right time, and public knowledge of stroke signs and symptoms is still quite poor. Many states are working on routing plans for emergency medical service providers, and we are still trying to decide which patients should go to a hospital that only provides IV lytic treatment versus those who should be routed to a hospital that has the capability of providing IA therapy. There is a need for more sophisticated...
cated clinical evaluation tools that could be used by emergency medical service providers to assess whether the patient has evidence of an LVO. Nonetheless, the progress toward minimizing the devastating effects of AIS is impressive, and there is only more good news coming.

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