The Endovascular Treatment of Acute Ischemic Stroke

In properly selected patients who are not IV tPA candidates, intra-arterial thrombolysis and mechanical embolectomy are viable therapeutic options.

BY ALEX ABOU-CHEBL, MD

Before 1995, there were no proven or approved treatments for acute ischemic stroke (AIS); since then, intravenous (IV) tissue plasminogen activator (tPA), intra-arterial (IA) recombinant prourokinase (r-pro-UK), and mechanical embolectomy have all been shown to be effective in the treatment of AIS or clot removal from the brain. Furthermore, a wide variety of endovascular techniques and devices are currently under investigation, offering hope for the more than 750,000 strokes that occur in the US annually.[1] Despite these advances, there remain major obstacles to the widespread use of the available therapies. The major limitation is the fact that all therapies for AIS have a significant risk of intracerebral hemorrhage (ICH). This complication, the most feared complication of AIS therapy, has no effective treatment and is fatal nearly 80% of the time. Furthermore, the heterogeneous nature of AIS makes treatment decision making complex and requires a thorough knowledge of cerebral physiology, pathophysiology, anatomy, and medical management.[2] Patient selection is perhaps the most important factor in determining a good neurological outcome, and this requires extensive clinical experience in stroke treatment.

PATHOPHYSIOLOGY

Ischemic stroke has many possible causes including cardiac embolism (20%), extracranial atherosclerosis/thrombosis (10%–12%), intracranial atherosclerosis (8%–10%), lipohyalinosis (25%–30%), aortic arch atherosclerosis (approximately 10%–20%), dissection (<5%), and hypercoagulable states (<5%), among others. The composition of thrombi causing acute arterial occlusion can therefore be quite varied, and most often the underlying vasculature is normal (a major difference compared to the vessels of patients with acute coronary syndrome). These variables need to be taken into consideration when making acute treatment decisions.

THE CEREBROVASCULAR CIRCULATION

The vessels most commonly involved in the etiology of clinically significant AIS are the intracranial internal carotid artery (ICA), the middle cerebral artery (MCA), the anterior cerebral artery (ACA), the intracranial vertebral artery (VA), the basilar artery (BA), and the posterior cerebral artery (PCA). The most common large vessel involved in AIS is the MCA followed by the ICA and the BA. The intracranial arteries are histologically different from other muscular arteries due to a lack of adventitia and external elastic lamina and the presence of a thin tunica muscularis. As a result, the vessels are easily perforated or ruptured during endovascular therapy. When this occurs, patients will develop either an ICH or—more commonly—a subarachnoid hemorrhage (SAH), both of which can lead to a rapid and marked elevation of intracranial pressure (ICP), cessation of cerebral blood flow, herniation and brainstem compression, and death.[3,4] Furthermore, reperfusion neuronal injury and cerebral hyperperfusion syndrome can complicate successful revascularization procedures and lead to neuronal death, cerebral edema, or hemorrhage; therefore, in some patients, revascularization should not be performed or should be delayed.

TREATMENT: AVAILABLE DATA

The current standard of care for the treatment of AIS is intravenous tissue plasminogen activator (IV tPA). This is, in fact, the only FDA-approved treatment for AIS and

TABLE 1. INDICATIONS AND CONTRAINDICATIONS FOR AIS ENDOVASCULAR THERAPY

Indications:
- AIS <6 hours in duration
- Stroke is significant (ie, disabling or life threatening)
- Suspected or known acute occlusion of a large artery (ie, nonlacunar stroke syndrome)

Contraindications:
- ICH is suspected or evident on CT
- CT scan shows evidence of acute ischemia in more than one third of the MCA territory
- History of ICH or subarachnoid hemorrhage
- The presence of an arteriovenous malformation or large thrombosed cerebral aneurysm
- Uncontrolled hypertension >185/110 mm Hg
- Profound hyperglycemia
- History of dementia of Alzheimer's type or known amyloid angiopathy
- Stroke duration is unknown or is >6 hours
- Recent stroke within 3 months (thrombolysis)
- Bleeding diathesis, elevated INR >1.7, or thrombocytopenia <100,000 cells/mm^3

AIS indicates acute ischemic stroke; CT, computed tomography; ICH, intracerebral hemorrhage; MCA, middle cerebral artery; INR, international normalized ratio.

must be given within 3 hours of stroke onset to minimize the risk of fatal ICH.[5] The bulk of published data on the endovascular approaches to acute stroke treatment is from small case series or nonrandomized safety studies, all of which have differed greatly in their methodologies and patient populations studied. As a consequence, there are no standardized or widely accepted endovascular techniques for the treatment of AIS, and many controversies remain, not the least of which is if treatment should be performed endovascularly.

The PROACT II study was the only randomized trial completed to date of IA thrombolysis for patients with AIS.[6] It randomized 180 patients with MCA occlusion to IA r-pro-UK versus placebo given within 6 hours of stroke onset. All patients received 2,000 U bolus of unfractionated heparin and 500 U/hour infusion for 4 hours. The r-pro-UK was infused over 2 hours at a fixed dose of 9 mg, irrespective of the clot burden, and mechanical disruption of the thrombus was not permitted. Compared to placebo, IA thrombolysis had superior recanalization efficacy with a 66% thrombolysis in myocardial infarction (TIMI) grade 2 or 3 recanalization rate compared to 18% in the placebo arm.[6] The TIMI 3 flow rate at 2 hours was only 19%; nevertheless, there was a 15% absolute benefit (58% relative benefit) for the treatment group over placebo in the number of patients who achieved a good functional outcome at 3 months as measured by the modified Rankin scale. The symptomatic ICH rate was 10% (for comparison, the ICH rate in the definitive IV tPA study that led to FDA approval was 6%).[5] The risks of IA lysis are therefore high but must be balanced against the natural history of untreated patients. In the population studied, MCA occlusion, the probability of good neurological outcome untreated is about 20%. Although the outcome of the PROACT II trial was positive, IA thrombolysis with r-pro-UK is not yet FDA approved due to an FDA demand for a larger confirmatory trial.[7]

Not all patients qualify for IV tPA therapy, and it is generally accepted that larger vessels and greater clot burdens (eg, occlusions of the ICA or BA) are more resistant to IV thrombolysis and that endovascular therapy is the best option for those patients; of note, there have been no randomized or direct studies of the clinical efficacy of IA compared with IV thrombolysis.[8,9] In combination with the PROACT II results, IA therapy for AIS has been considered by some as an appropriate therapeutic option for selected patients who are not candidates for IV tPA (eg, patients with recent noncerebral hemorrhage, major organ surgery or arterial puncture in a noncompressible site, patients on systemic anticoagulation, and those presenting between 3 to 6 hours after stroke onset).[10]

Because r-pro-UK is not commercially available and no randomized trials have compared IA therapy with best medical treatment for AIS, clinicians must rely on the available anecdotal published data. A recent meta-analysis of 27 reports of IA lysis with a total of 1,117 patients compared treatment results against prognostic models of natural history adjusted for National Institutes of Health Stroke Scale (NIHSS) scores and age. The combined data showed that there was no net benefit for IA thrombolysis, with percent differences from predicted outcomes varying from -51% to 24.6% for mortality and -30.3% to 28.7% for good functional outcome. There was, however, an indication that the use of lower doses of thrombolytics (urokinase in particular) was associated with better outcomes. Such analyses are inherently flawed but are nevertheless helpful and emphasize the need for prospective trials of IA thrombolysis.

ADJUNCTIVE PHARMACOTHERAPY

In a few small reported series, platelet glycoprotein (GP) IIb/IIIa receptor antagonists have been used successfully in combination with thrombolytics to treat patients with

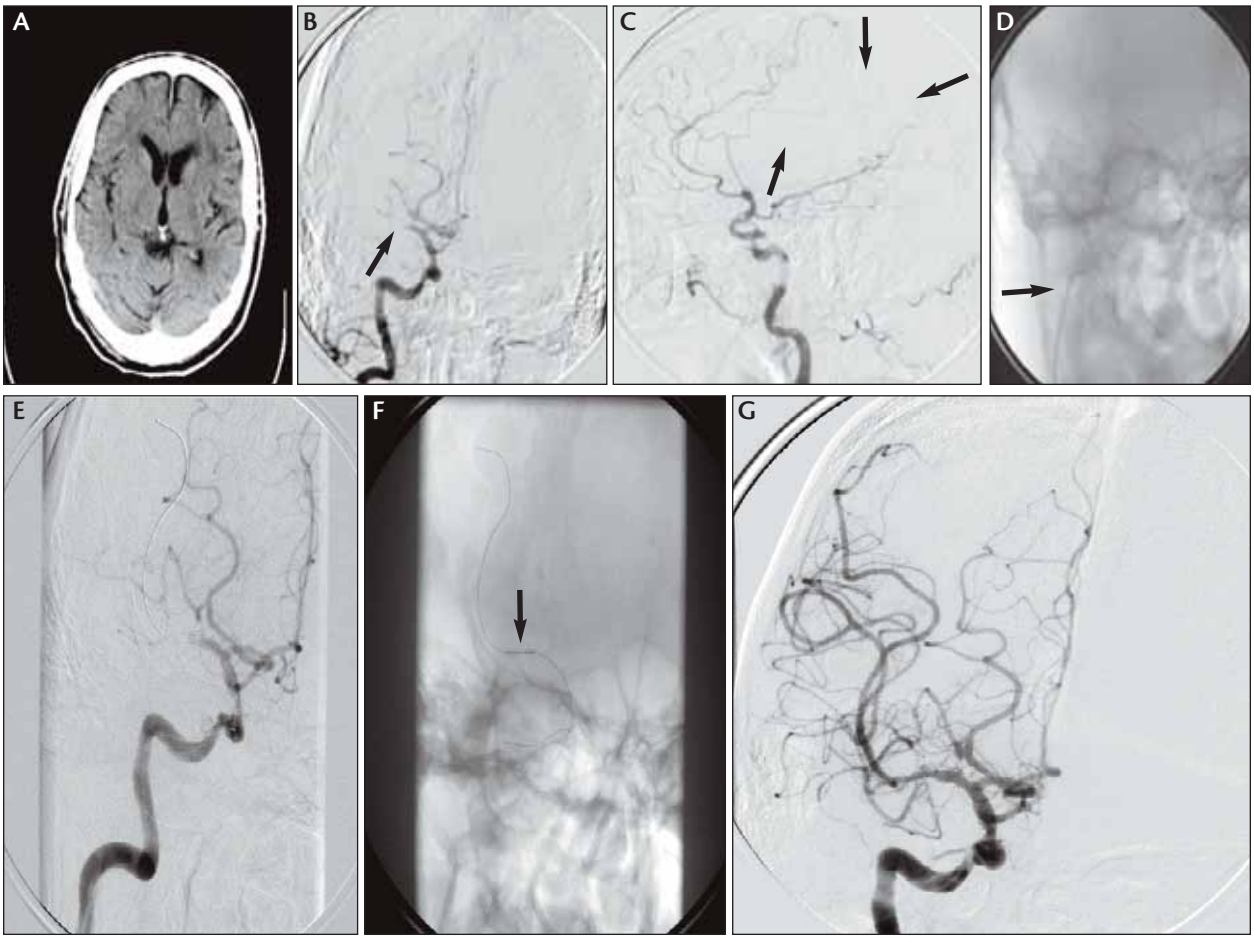

Figure 1. A 71-year-old man with a history of hypertension, hyperlipidemia, and cigarette smoking presented 4 hours after onset of a dense left hemiparesis, hemianopsia, and right gaze deviation. His NIHSS score was 18, consistent with a right MCA. A non-contrast CT of the brain showed no evidence of acute ischemia (A). Emergent angiography was performed revealing a mid-right MCA trunk occlusion (arrow), which is best seen in the anteroposterior cranial view (B). The lateral image does not show the site of occlusion but shows the anterior and posterior cerebral artery territories well, and the lack of flow to the MCA cortical branches (arrows) (C). A 6-F guide catheter could only be advanced into the midcervical internal carotid due to the tortuosity (arrow) (D). Through the guide, a 2.3-F microcatheter was advanced over a .014-inch wire into the thrombus, and through it, 25 mg of tPA was infused over 30 minutes with no improvement in flow (E). The microcatheter was exchanged over the wire for a 1.5- X 9-mm balloon that was used to angioplasty the MCA twice. A waist (arrow) is clearly seen on the balloon, suggesting the presence of an underlying atherosclerotic lesion rather than an embolism (F). Partial recanalization was achieved, but the vessel reoccluded almost immediately. Therefore, the balloon was exchanged for the microcatheter through which 6 mg of abciximab was infused into the MCA. This was followed by almost immediate recanalization, although an underlying stenosis is clearly visible on the final anteroposterior angiogram (G). The flow was markedly improved, so no further intervention was performed. The patient was monitored closely without additional antithrombotics for 24 hours and made a nearly complete recovery.

AIS without significantly increasing the risk of ICH.[11,12] The GP IIb/IIIa antagonists are typically infused IV, but IA administration directly into the thrombus through the microcatheter may facilitate thrombolysis by saturating the platelets within the thrombus.[12] A continuous (12-hour) infusion should rarely be considered after successful thrombolysis because in a randomized trial of IV abciximab, there was an excessive risk of ICH.[13]

ADJUNCTIVE CLOT DISRUPTION

Adjunct balloon angioplasty for acute stroke has been reported both in combination with other techniques and as the sole treatment.[12,14-16] When contemplated, the balloons should be undersized to avoid vessel rupture, and it is always the rule that they should never be oversized. In some circumstances, angioplasty is inadequate, and stenting of the occluded vessel may be needed if patients

have a severe underlying stenosis, either of the intracranial or extracranial vessel.[17] This approach should not be considered as a standard of care, but in selected patients, it can probably be performed with a low risk of ICH.

CLOT EXTRACTION

Under some circumstances, IA thrombolysis may be contraindicated (eg, active systemic bleeding), associated with a high risk of ICH (eg, early infarct signs or recent neurosurgery), or ineffective. Thrombolysis, even given IA, may be slow to recanalize an artery, and whereas many neurointerventionists do not infuse lytics over 2 hours (as was done in PROACT II), most give lytics over 30 to 60 minutes. As a result, when the time to achieve lesion access is considered, several hours may pass between the time that the decision to treat with IA was made and vessel recanalization, during which formerly salvageable brain tissue may be irrevocably lost. Mechanical embolectomy, or clot removal, is an emerging adjunct/alternative to thrombolysis that may greatly increase the speed of recanalization. Several devices for mechanical embolectomy have been or are being developed. In August of 2005, the FDA approved the first device for clot removal, the Merci Clot Retriever (Concentric Medical, Inc., Mountain View, CA). The Merci retriever system consists of a helical nitinol wire tip, a microcatheter, and a balloon occlusion guide catheter. The device is passed through the microcatheter distal to the thrombus; the clot is then snared in the wire helix and withdrawn from the vessel under negative pressure applied through the balloon occlusion guide catheter. The device was initially available in two models: the stiffer X6 and the softer X5. The system was approved based on the data from the single-arm MERCI (Mechanical Embolus Removal in Cerebral Ischemia) trial in which 151 patients with various large-vessel occlusions were enrolled.[18] A device could be deployed in only 141 patients in whom recanalization was successful in 45%. With adjunctive thrombolytics, another 11.3% were recanalized. The incidence of symptomatic ICH was 8%. The overall mortality rate at 90 days was 39%, a rate driven primarily by patients who could not be revascularized who had 61% mortality. Good outcomes were achieved in only 28% of patients, which was close to the placebo arm of PROACT II. As a result, the FDA approved the device for the "removal of clots" and not for stroke therapy.

Newer generations of the Merci device have since been developed. First came the "L-series" of retrievers (L4, L5, L6, increasing in size and stiffness), which have a 90º bend at the junction of the wire and the helix and several suture-like filaments attaching the distal end of the helix with the proximal end. The L5 series was tested in the Multi MERCI trial, which was a prospective, single-arm trial of patients treated within 8 hours of symptom onset that also included patients who had failed IV tPA.[19] One hundred sixty-four patients were enrolled, of which 131 were initially treated with the L5 Retriever. Successful recanalization was achieved in 57.3% of treatable vessels and in 69.5% after adjunctive IA thrombolysis. Favorable clinical outcomes were seen in 36%; mortality was down to 34%, and symptomatic ICH occurred in 9.8% of patients. Clinically significant procedural complications occurred in 5.5% of patients. The rates of good clinical outcomes trended higher than historical controls. Although the clinical outcomes in the MERCI trials are not adequate to prove that mechanical embolectomy is effective in the treatment of AIS, they did show that revascularization was an independent predictor of favorable outcome (odds ratio [OR], 12.82; 95% confidence interval [CI], 2.95–55.75) and lower mortality (OR, 0.33; 95% CI, 0.14–0.77). Yet another generation of Merci retrievers has recently been released: the "V series," which is similar to the L series but without the 90º bend proximal to the helix. It is touted as having recanalization rates of 70%, but no data are yet available to support this claim.

The second mechanical embolectomy device, the Penumbra system (Penumbra, Inc., Alameda, CA), received FDA approval in early 2008 to reduce clot burden within 8 hours of AIS. This system consists of a series of three variously sized microcatheters, a "separator wire," and a continuous suction device that applies 1 atmosphere of suction through the microcatheter. The separator wire acts as a shear as it is moved in and out of the tip of the microcatheter to break up the thrombus as it enters the microcatheter so that it can be aspirated out of the artery. The major difference between this system and the Merci system is that access to the thrombus and vessel is not lost with every pass of the device. The single-arm Penumbra study enrolled 125 patients with AIS under 8-hour duration with an 82% revascularization efficacy rate. Nearly 42% of patients had a favorable outcome, defined as improvement of four points or more on the NIHSS at discharge, or a 30-day modified Rankin score of two points or less. Although it would appear that the Penumbra system is superior to the Merci system, the patient populations treated in the Penumbra study and the MERCI trials are not comparable, and the definitions of recanalization were different. Therefore, a direct comparison is not possible until it can be performed in a randomized trial.

PATIENT SELECTION

Patient selection is the most complex and critical aspect of endovascular AIS treatment. Treating a patient with a nondisabling stroke and treating one with nonsal-

vageable tissue will greatly increase the risk of neuronal injury, disability, ICH, and death. All patients should be evaluated clinically by a physician expert in the diagnosis of AIS. The time of stroke onset must be known with certainty before an intervention can be performed, because the duration of ischemia is a predictor of prognosis and the risk of ICH.[20,21] In most circumstances, 6 hours appears to be the upper limit for safe intervention; however, longer durations of ischemia may still be treatable in appropriately selected patients.[22,23] Of course, the earlier that treatment can be started the better the prognosis.[24]

Before any treatment can be initiated, cerebral imaging with a nonenhanced computerized tomographic (CT) scan of the brain must be performed in all patients, without exception. CT is currently the standard means of evaluating the brain in the setting of AIS, primarily because of its high sensitivity and specificity for ICH. Magnetic resonance imaging (MRI), CT angiography, and CT perfusion studies may also be considered in some or all patients and are of great value in decision making by permitting an assessment of the size of the ischemic core and ischemic penumbra to maximize the benefit and minimize the risk of reperfusion therapy.[25-28] The best means of differentiating ischemic core from penumbra is not yet clear, and a full discussion of the merits of these modalities is far too complex to be discussed briefly and is beyond the scope of this review. An expert in stroke should therefore be involved to determine the best imaging study and to determine which patients are candidates for intervention.

A history of ICH or any other factor that would increase the risk of ICH or systemic hemorrhage are generally the contraindications to IA thrombolysis. Factors such as patient age greater than 80 years, elevated serum glucose level, active treatment with heparin or a heparinoid, therapy with high-dose aspirin, clopidogrel, or platelet GP IIb/IIIa receptor antagonists should also be considered as relative contraindications.[20,29] Table 1 lists the indications and contraindications to IA therapy for AIS.

INTERVENTIONAL APPROACH

Several approaches to achieve recanalization have been described. Most of the published series have reported on the use of thrombolytics alone similar to the PROACT II protocol but without the use of r-pro-UK.[30] More recently, some investigators have reported on the use of a combination of pharmacological agents, while a few series have described a purely mechanical approach.[11] A multimodal approach combining multiple pharmacological agents and mechanical disruption may be superior to a single-modality approach because of the heterogeneity of AIS[12,31] (eg, not all thrombi are composed of the same platelet and fibrin components and not all emboli are thrombi). Therefore, the treatment approach should be adjusted to the needs of each patient (Figure 1). For example, in patients with a high likelihood of cardioembolism as the cause of the stroke, higher doses of thrombolytics may be preferred, whereas in patients with an atherothrombotic lesion, GP IIb/IIIa inhibitors may be combined with thrombolytics and angioplasty or even stenting alone. However, in standard clinical practice, the first-line treatment remains the infusion of a single thrombolytic agent. The technique of IA therapy varies widely between different interventionists including differences in the choice of pharmacological agent as well as the dose, the rate of infusion, and the duration of the infusion.

The most widely used thrombolytic agent is tPA,[32,33] but other agents have also been used including urokinase, reteplase, and tenecteplase.[11,34,35] Although tPA is the most commonly used, there are data suggesting that it may not be ideal because it has some neurotoxic effects and may be associated with higher risks of ICH.[36] The optimal dose of each agent is unknown, but, in general, lower doses are preferred, and excessive dosing may not only increase the risk of ICH, it may also lead to a paradoxical increase in thrombosis. The presence of patient characteristics that are associated with higher risks of ICH or poor prognosis should limit the dose of thrombolytics given; these include but are not limited to increasing patient age, hypertension >185/110 mm Hg, elevated serum glucose, duration of ischemia >4 hours, the absence of collateral blood flow, underlying large brain infarct greater than one third of the MCA territory, or large clot burden (eg, complete ICA occlusion from bulb to MCA).[37]

PERIPROCEDURAL MEDICAL MANAGEMENT

A complete discussion of medical vascular neurology and neurological critical care are beyond the scope of this review; only a cursory discussion of the most pressing matters will be discussed. Blood pressure (BP) control is the most important periprocedural clinical factor due to the impairment of cerebral autoregulation during and after ischemic conditions. Elevations of mean arterial pressures may lead to marked elevations of cerebral blood flow and an increased risk of reperfusion injury and ICH. The optimal range for BP varies for each patient, but, generally speaking, after pharmacological thrombolysis, BP should be kept <185/110 mm Hg. In general, it is preferable not to lower arterial BP before recanalization is achieved unless the BPs are significantly elevated (ie, >220/130 mm Hg).[38] It is critical to keep in mind that the prevention of ICH is the single most important task after any cerebral intervention because ICH has no effective treatment and is fatal in up to 80% of cases. The management of poststroke and ICH patients can be complex and

is best performed with the assistance of an experienced neurointensivist and stroke neurologist.

UNRESOLVED ISSUES

In addition to the lack of data supporting the safety and efficacy of IA therapy and mechanical embolectomy, and the superiority of one approach versus the other, there are unresolved issues revolving around postprocedural care, use of anticoagulants after intervention, and appropriate methods of minimizing reperfusion injury and ICH. The treatment of patients who are beyond the 6-hour window and those who have early ischemic changes on CT are very controversial. In addition, there is a lack of reimbursement for physician professional fees, both for IV and IA therapy, despite the new stroke diagnosis-related group codes.

CONCLUSION

Endovascular treatment of AIS remains very complex, with the continuous need to balance between the drive to achieve rapid recanalization and the risk of ICH. Management of these patients requires a thorough understanding of the intracranial cerebral vasculature and the pathophysiology of stroke. Although more randomized controlled trials are needed to help find the most efficacious treatment strategy, IA lysis, with or without thrombectomy, appears to be an effective recanalization strategy with the potential for greatly improving neurological outcomes. ■

Alex Abou-Chebl, MD, is Director, Neurointerventional Services; and Associate Professor, Neurology and Neurosurgery at the University of Louisville, School of Medicine, Louisville, Kentucky. He has disclosed that he has received honoraria for the speaker's bureau of Bristol-Myers Squibb/Sanofi-Aventis. Dr. Abou-Chebl may be reached at (502) 852-7642; a0abou03@louisville.edu.

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