Emerging Therapies for Cerebrovascular Disorders

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Several important advances were reported over the past year that impacted on emerging therapies for cerebrovascular disorders. In addition to therapies directed at the acute treatment and prevention of ischemic stroke, trial results of treatments for intracerebral hemorrhage (ICH) also were reported. This brief review will focus on the most important recent stroke therapy reports.

ICH is a devastating disease that currently has no effective medical treatment. Surgical evacuation typically is considered in younger patients with lobar hemorrhages and a deteriorating clinical course, but the role of surgery remains controversial.1 Two recent reports provide important new information to guide clinicians in this therapeutic area. The International Surgical Trial in Intracerebral Hemorrhage (ISTICH)2 randomized >1000 patients to “early surgery” of the hematoma or “initial conservative treatment.” Patients were included if they had a spontaneous supratentorial ICH within 72 hours from symptom onset and there was clinical uncertainty as to the need for surgical evacuation. The 2 groups were well balanced and the hemorrhages were located in basal ganglia or thalamus in 50% of cases. More than 25% of patients who were randomized to initial conservative treatment later went on to surgery because of neurological deterioration. Favorable outcome at 6 months, based on change of a dichotomized prognosis at time of presentation calculated according to illness severity, was achieved by 26.1% of patients in the early surgery group and by 23.8% in the initial conservative treatment group (odds ratio, 0.89; 95% CI, 0.66 to 1.19). There was no difference in mortality rate, and subgroup analyses did not identify any category significantly associated with benefit from early surgery. These results confirm that there is no evidence to support a policy of early surgery in patients with spontaneous supratentorial ICH. However, more than two thirds of screened patients, neurosurgeons expressed certainty about treatment, and in one third of them, surgery was performed, particularly in younger patients with lower Glasgow Coma Scale score and a lobar location.3 Consequently, further analysis will be needed to determine whether patients treated outside the trial had a better outcome and to limit the confounding effects of those patients.

In contrast to the neutral results of ISTICH, preliminary data of a recent phase IIIB clinical trial suggest that ultraearly hemostatic therapy in spontaneous ICH may reduce the volume of the hematoma and improve outcome (Stephan A. Mayer, Fifth World Stroke Congress, Vancouver, Canada, 2004). In this study, 400 patients scanned within 3 hours of hemorrhage onset were randomized to receive 3 different doses of recombinant activated factor VII (rFVIIa) or placebo within the next 60 minutes. The treatment was administered as a single intravenous bolus. The primary end point of mean percent change in ICH volume at 24 hours was 29% in the placebo group and 16%, 14%, and 11% in the 40, 80, and 160 μg/kg dose groups (P<0.0175; overall test for trend). Patients treated with rFVIIa showed a nonsignificant 34% to 38% relative reduction in mortality. Favorable global functional outcome at 3 months, defined as a modified Rankin Scale 0 to 3, was achieved by 31% in the placebo group and by 45%, 51%, and 46% in the rFVIIa groups (P<0.05 for all comparisons). Active treatment significantly increased by 2.1- to 2.4-fold the odds of favorable outcome after controlling for age, volume, and location of ICH at baseline. These results indicate that ultraearly hemostatic therapy with rFVIIa can limit ongoing bleeding in acute ICH.4 However, thromboembolic serious adverse events were more frequent in patients treated with rFVIIa (6%, 4%, and 10%) than in those who received placebo (2%; P=0.12), a finding that raises concerns about the safety of the drug. A phase III trial will start soon to clarify the risk/benefit ratio of rFVIIa in early ICH patients.

Concerning new therapeutic developments for ischemic stroke, the final results of the Desmoteplase in Acute Stroke (DIAS) trial5 and unpublished preliminary data of the Mechanical Embolus Removal in Ischemic Stroke (MERCI) trial that led to Food and Drug Administration (FDA) approval are important. In the dose-finding phase II DIAS study, 104 patients were randomized between 3 and 9 hours after stroke onset to receive desmoteplase or placebo if they had a National Institutes of Health Stroke Scale score of 4 to 20 and the baseline MRI showed a perfusion/diffusion mismatch ≥20%. Because of an excessive rate of symptomatic ICH (26.7%) in the first 30 patients treated with fixed doses of desmoteplase, lower weight–adjusted doses escalating through 62.5, 90, and 125 μg/kg were investigated subsequently. In this part of the study, desmoteplase showed a very reasonable safety profile because symptomatic ICH occurred 26.1% of patients in the early surgery group and by 23.8% in those who received placebo (2%; P=0.12), a finding that raises concerns about the safety of the drug. A phase III trial will start soon to clarify the risk/benefit ratio of rFVIIa in early ICH patients.
in 2.2% of treated patients and in no placebo patients. Reperfusion, defined as either ≥30% reduction of perfusion lesion volume or ≥2 points improvement on magnetic resonance angiography grading scale 4 to 8 hours after treatment, was observed in 71.4% of patients treated with desmoteplase (125 μg/kg) compared with 19.2% with placebo (P=0.0012). Favorable outcome at 90 days, based on a combined analysis of neurologic and functional scales, was achieved by 22.2% of patients in the placebo group and by 13.3% (62.5 μg/kg; P=0.757), 46.7% (90 μg/kg; P=0.053), and 60.0% (125 μg/kg; P=0.009) of patients treated with desmoteplase. Importantly, a longer delay from onset to treatment was not associated with a reduction of treatment effect, suggesting that beyond 3 hours, tissue at risk identified by perfusion/diffusion mismatch is a better predictor of response than the duration of symptoms. A pivotal efficacy study is currently being planned.

The recent approval of the Merci Retriever by the Center for Devices and Radiological Health at the FDA for the removal of clots from the intracranial vasculature of ischemic stroke patients raises important issues and concerns.\(^8\) It must be emphasized that this approval was not for treatment of ischemic stroke but for the mechanistic process of clot removal and reperfusion. The approval was based on the results of the MERCI trial of 114 acute ischemic stroke patients who underwent device implementation within 8 hours of stroke onset. The results in these patients were compared with the placebo group of the PROACT II study that evaluated intra-arterial prourokinase.\(^7\) Serious adverse events occurred in 3.5% of the MERCI patients (2 patients had arterial perforation with fatal hemorrhage and 2 other patients had a stroke in an uninvolved territory). The rate of symptomatic ICH was 8%, compared with 1.8% in the PROACT placebo group. The primary end point of partial or complete recanalization rate was 53.5% in MERCI and 18% in the PROACT placebo group. Clinical outcomes were a secondary end point and demonstrated no significant difference compared with historical controls, although the baseline stroke severity was slightly worse in MERCI patients. Despite reservations about the trial data expressed by an advisory panel, approval for clot removal was granted for use in the United States. At this time, it remains unclear whether this approved device is indeed safe or effective in acute ischemic stroke, and further studies are needed to address these issues before widespread use can be endorsed.

Several important advances occurred recently concerning various approaches to stroke prevention. It is well established that carotid endarterectomy (CEA) is beneficial for preventing strokes in symptomatic patients with >70% ipsilateral carotid stenosis and in subgroups of patients with >50% stenosis.\(^8\) The value of CEA compared with medical therapy in asymptomatic patients with carotid stenosis is less clear and was primarily based on the Asymptomatic Carotid Atherosclerosis Study (ACAS) published in 1995.\(^10\) The Asymptomatic Carotid Surgery Trial (ACST) provides further illumination for this somewhat vexing clinical problem.\(^11\) In this study, 3120 asymptomatic patients with ≥60% carotid stenosis identified during ultrasonography were assigned to immediate CEA or deferral of surgery and were followed for a mean period of 3.4 years. The risk of stroke or death within 30 days of CEA was 3.1% in the CEA group and 0.8% in the deferral group, whereas 5-year risks of nonpreoperative stroke were 3.1% and 11%. (P<0.0001). When the preoperative and nonperioperative stroke risk was combined, a highly significant 5.4% absolute risk reduction occurred, very similar to the ACAS results. The benefits were similar in males and females and were not substantially different with varying degrees of carotid stenosis. In patients >74 years of age, benefits for CEA were uncertain. A combined analysis of ACAS and ACST suggests that CEA in asymptomatic patients with >60% carotid stenosis affords a small but significant overall benefit if the surgery can be performed with low preoperative morbidity and mortality rates.\(^12\)

A second important issue related to carotid artery stenosis and stroke prevention is the comparative utility of CEA and carotid angioplasty/stenting. In the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) study, high-risk symptomatic and asymptomatic stenosis, >50% symptomatic and >80% asymptomatic stenosis by carotid ultrasound, were assigned randomly to CEA or angioplasty/stenting with an emboloprotection device if the investigative team at each site agreed that either procedure was potentially feasible and safe.\(^13\) Of the 747 patients enrolled in the study, only 334 were randomized. Of the nonrandomized patients, 406 underwent stenting and only 7 CEA because 1 procedure was not felt to be appropriate. In the randomized patients, 20 of 167 (12.2%) had a primary end point event stroke, death, or myocardial infarction within 30 days or ipsilateral stroke within 31 days to 1 year. The primary event rate was 32 of 167 (20.1%) in the CEA group (P=0.004 for noninferiority). The SAPPHIRE study appears to demonstrate that angioplasty/stenting is at least equivalent and maybe superior to CEA in high-risk patients with carotid stenosis. Additional studies will be necessary to provide more precise guidance as to when to best use 1 intervention or the other.

Concerning medical therapy to prevent stroke, the recently reported Management of Atherothrombosis with Clopidogrel in High-risk patients (MATCH) study was the most important new study in 2004.\(^14\) In MATCH, 7599 transient ischemic attack or stroke patients with at least 1 other vascular risk factor were randomized to 75 mg per day Clopidogrel or 75 mg per day Clopidogrel plus aspirin. The primary end point was ischemic stroke, myocardial infarction, vascular death, or rehospitalization for an acute ischemic event. Follow-up data on 7276 patients were available at 18 months. The primary outcome event rate was 16% in the combined treatment group and 17% in the Clopidogrel-alone group (P=0.244), and the stroke rate was 8% in both groups. The rates of life-threatening bleeding were 3% in the combined therapy group and 1% in the Clopidogrel-alone group (P<0.0001). The MATCH study demonstrates that combining Clopidogrel and aspirin in high-risk cerebrovascular patients did not significantly reduce secondary events and was associated with a highly significant risk for life-threatening bleeding.

References


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