

Current Status of Hemorrhagic Stroke and Acute Nonthrombolytic Ischemic Stroke Treatment

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Strokes still cause death every 3.3 minutes in the United States and are a leading cause of disability. Although the thrombolytic tissue plasminogen activator has been available for the treatment of ischemic stroke since 1996, no neuroprotectant acute stroke treatment strategy to preserve dysfunctional neurons in the ischemic penumbra has shown efficacy in clinical trials. New approaches for the treatment of hemorrhagic stroke and changes in the design of acute ischemic stroke trials provide a more optimistic picture for future stroke treatments.

Hemorrhagic Stroke

Hemorrhagic stroke has received far less attention than ischemic stroke. Hemorrhagic stroke offers >1 potential approach for treatment, some of which are only now being assessed in clinical trials. These include preventing hematoma expansion, reducing any perihemorrhage oligemia, and preventing hemorrhage recurrence.

The International Surgical Trial in Intracerebral Hemorrhage (STICH) was the first multicenter trial to assess the efficacy of early surgical evacuation of hemorrhage. This trial, reported in February 2004, required that patients be randomized to surgery or conservative treatment by 96 hours after the ictus.¹ Perhaps because the trial allowed both superficial and deep hemorrhage locations to be included, it showed a neutral effect for surgery.

Although seemingly counterintuitive to the treatment of hemorrhage, the use of a lytic was also reported in February 2004. In an early safety trial in patients with intraventricular hemorrhage, low-dose tissue plasminogen activator was injected into the ventricles to reduce clot burden.² Although high adverse event rates will require careful planning of future trials, encouraging trends toward improved functional outcomes were seen.

A trial comparing activated recombinant factor VII (NovoSeven) administered intravenously to placebo provides another way to try to prevent hemorrhage expansion (Novo Nordisk). The phase IIb trial completed enrollment in March 2004. Compared to the placebo group, treated patients had a reduction in hematoma growth at 24 hours as measured by computed tomography (Novo Nordisk).

Whether perihematoma ischemia exists has been a matter of debate. A recent magnetic resonance imaging study showed increased rates of water diffusion in the perihematoma region, suggesting the edema is plasma-derived and not related to ischemia.³ Patients with hemorrhagic strokes were included in the CLASS H subgroup of the multicenter clomethiazole (Astra Pharmaceuticals) neuroprotection trial reported in 2000.^{4,5} Clomethiazole is a gamma-aminobutyric acid A receptor agonist that reduces depolarization by increasing chloride conductance. In the CLASS H safety study, mortality rates were higher in the clomethiazole-treated patients than in the placebo cohort ($P=0.08$). Because more patients in the treatment group were taking warfarin, however, the cause of the increased mortality was unclear.

A National Institutes of Neurologic Disorders and Stroke (NINDS) workshop, titled Priorities for Clinical Intracerebral Hemorrhage Research, was held in November 2003 to advise the institute about the future of acute intracerebral hemorrhage research. The 29 participants took part in 6 study groups: the current state of intracerebral hemorrhage research and patient care; basic science; medical therapy; surgical therapy; imaging; and clinical methodology challenges. The findings of the workshop have been submitted for publication.

The greatest strides in reducing disability from hemorrhagic strokes may come from their prevention. In addition to a renewed focus on blood pressure treatment to prevent hypertensive hemorrhages and innovations in the treatment of vascular malformations, the prevention of hemorrhagic strokes caused by cerebral amyloid angiopathy has entered the treatment arena. Safety data for the phase II study (jointly funded by the NINDS and Neurochem, Inc) of Cerebril, a drug that may help to prevent amyloid deposition as one of its mechanisms, was presented in April 2004.⁶ Although dose-dependent nausea and vomiting were seen, no significant safety issues were identified. The drug showed good oral absorption and detection in the cerebrospinal fluid. Efficacy trials are planned.

Acute Ischemic Stroke

All clinical neuroprotection trials in ischemic stroke have failed to show efficacy thus far. These include agents that

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work on early steps in the ischemic cascade, such as those blocking or modulating receptors or ion channels to reduce excitatory neurotransmitter release,^{5,7–11} and those drugs that act on later ischemic events, like leukocyte adhesion blockers and membrane stabilizers.^{12,13} Some of these trials had treatment windows exceeding 6 hours.^{5,13} Others treated patients with mild symptoms or no cortical signs, excluding patients with the gray matter tissue most likely to contain the receptors targeted by the drugs.^{9–11} The spontaneous improvement in these patients with mild symptoms also potentially diluted the benefits seen from treatment. In the Intravenous Magnesium Efficacy in Stroke trial, however, patients without cortical strokes paradoxically showed more benefit than those with cortical features.¹¹ Although this could be because of an effect of magnesium on white matter ischemia, it may also be the result of unrelated factors.¹¹

Many current trials have included patients with symptoms lasting <6 hours and have limited enrollment to those with moderately severe strokes and cortical signs. In addition, most of the current trials allow the concurrent use of lytics to increase perfusion and help the neuroprotective strategies to succeed.^{14,15} Such phase III trials currently in progress include an inhibitor of abnormal astrocyte activation, ONO-2506 (Ono Pharmaceuticals), a serotonin agonist, repinotan (Bayer Corporation) (completed enrollment in June 2004), and a free radical scavenger, NXY-059 (Astra Zeneca), although the free radical scavenger trial requires significant weakness but no cortical signs. However, an agent assessed in 2 international trials that enrolled patients with cortical signs within 6 hours has already shown negative results. The agent, BMS-204352 (Bristol-Myers Squibb), is a maxi-K channel modulator.¹⁶

The future of neuroprotection trial design has already arrived with the advent of the Field Administration of Stroke Therapy–Magnesium (FAST-MAG) Phase III clinical trial, in which treatment is given earlier than in any trial to date.¹⁷ In this ongoing study, paramedics administer a loading dose of magnesium sulfate or matched placebo in the field to patients with a deficit that has been present for at least 15 minutes but <2 hours.

The Stroke Therapy Academic Industry Roundtable (STAIR) has met 4 times since 1999 to provide guidelines for the evaluation of candidate drugs in an effort to increase the chances of identifying a successful one. Recommendations for preclinical models have included obtaining adequate dose-response curves, performing time window assessments at delayed time points, and assessing the drug in >1 species.¹⁴ More recent STAIR clinical guidelines suggest identifying agents and patient subgroups, especially through imaging, that allow for later intervention, considering multimodal approaches using mechanical and thrombolytic techniques or >1 neuroprotectant, and increasing the efficiency of trials by considering the formation of consortia and centralized databases.¹⁵

The implementation of trial design changes and careful selection of endpoints offers optimism that a neuroprotectant will show efficacy. Ongoing identification of novel mechanisms of treatment provides further hope for stroke patients.

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