

abundance of calcium ions to rush in, which in turn causes the release of even more glutamate. The continuous glutamate receptor stimulation and massive influx of calcium ions are not without consequence, eventually leading to activation of various degradative enzymes inside of the cell. These enzymes lead to the destruction of the cell membrane, which ultimately kills the cell, releasing toxic free radicals, even more glutamate, and other substances that can cause further damage to the surrounding brain tissue.

There has been little progress over the past decade in the treatment of ischemic stroke. The last product to receive FDA approval for the treatment of ischemic stroke was Genetech's Activase in 1996. It is estimated that over the past decade more than 50 compounds have failed in clinical development for the treatment of stroke. Notable failures include glutamate and NMDA receptor antagonists, which were heralded for a time as the next potentially big thing in stroke treatment. While successful drug development in the stroke arena has been a challenge, there are a few products under development that could prove to be valuable additions to the ischemic stroke treatment armamentarium.

STAIR Guidelines Help Direct Stroke Drug Development

Because of the poor track record for stroke drug development, the STAIR (Stroke Therapy Academic Industry Roundtable) group was formed in the late 1990s. In 1999, the group published criteria for advancing product candidates for the treatment of stroke into clinical trials. The criteria include adequate dose-response and serum concentration measurements; confirmation of efficacy in relevant time windows; the use of physiological and behavioral outcome measures in animal studies instead of only infarct size; use of multiple types of stroke models; trials in larger species; and reproducibility of preclinical results by independent laboratories. Although meeting the STAIR criteria does not guarantee clinical success, our consultants believe that it does decrease the likelihood of failure.

Modified Rankin Scale Viewed As Best Measure Of Efficacy

There are a number of different clinical outcome measures used in clinical trials for stroke drugs including the Barthel Index Score (BIS), Modified Rankin Scale (MRS), Glasgow Outcome Scale, and the NIH Stroke Scale (NIHSS). Our consultants indicate that the Modified Rankin Scale has emerged as the standard for judging the efficacy of stroke drugs for several reasons. First, the MRS is clinically meaningful as it evaluates disability, or how much assistance a person would need to live life. The MRS scores patients on a scale from 0 to 6, with 0 being asymptomatic and 6 being dead. Scores of 0-2 are considered "good" stroke outcomes; in that these patients are able to lead fairly independent lives and are able to return to work in almost all cases. Scores of 3 or greater indicate that the patient will need considerable help with their daily activities. As defined, improvement in MRS score translates relatively clearly into improvements in patients' quality of life. The NIHSS, on the other hand, is more a measure of neurocognitive function, and therefore its correlation to clinical benefit is less direct. Patients are given a neurologic exam, and tested on gross abilities (can they speak, do their arms move, do their legs move, etc). Second, the MRS has emerged as the gold standard because there is much less variability in physician assessments using it compared to the NIHSS. Our consultants believe that virtually any two physicians would score a patient the same using the MRS, but that is not always the case using the NIHSS.

Modified Rankin Scale (MRS) vs. NIH Stroke Scale (NIHSS)

MRS		NIHSS	
Score	Criteria	Score*	Criteria
0	Asymptomatic	0-3	Level of consciousness (general)
1	No significant disability despite symptoms; able to carry out all usual duties and activities	0-2	Level of consciousness (questions)
		0-2	Level of consciousness (commands)
		0-2	Best gaze
2	Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance	0-3	Visual fields
		0-3	Facial palsy
3	Moderate disability; requiring some help, but able to walk without assistance	0-4	Motor arm (each arm gets scored)
		0-4	Motor leg (each leg gets scored)
4	Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance	0-2	Limb ataxia
		0-2	Sensory
		0-3	Best language
5	Severe disability; bedridden, incontinent and requiring constant nursing care and attention	0-2	Dysarthria
		0-2	Extinction and inattention
6	Death		

*Individual scores for each NIHSS criterion are summed to a final score. Higher values correlate with worse symptoms.

Source: NIH website

Current, Potential, & Failed Treatments For Acute Stroke

Activase (Genentech)

Activase (tissue plasminogen activator; tPA) is a thrombolytic that works by helping to dissolve the blood clot causing the ischemic stroke, thereby restoring blood flow to the affected region of the brain. In pivotal clinical trials, treatment within three hours of stroke onset was at least 33% more likely to result in minimal or no disability at three months post stroke vs. placebo. However, Activase has several major shortcomings that have limited its market opportunity. Because Activase works by dissolving the stroke-causing clot, it has a limited therapeutic window and must be given within three hours of the onset of the stroke. In fact, Activase failed in two trials designed to test an extended treatment window of five to six hours. Additionally, Activase is only indicated for ischemic strokes, and can be dangerous if given to a patient with a hemorrhagic stroke. All patients are required to have a CT scan to rule out intracranial or subarachnoid hemorrhage prior to the initiation of therapy with Activase. Because of an increased risk of bleeding, Activase is contraindicated in patients who have had recent (within three months) intracranial or intraspinal surgery, serious head trauma, or a previous stroke. Even when it is administered correctly, 6% of patients suffer intracerebral hemorrhage after receiving Activase. With all of its limitations and restrictions, Activase is administered to approximately 2-3% of stroke patients. Two pivotal trials were completed in support of Activase's approval (NINDS-Part 1 & 2). NINDS-1 evaluated the effects of Activase at 24 hours and three months following treatment. While no difference versus placebo was seen at 24 hours; neurological improvement was seen at three months as measured by the Barthel Index Score (score \geq 95), Modified Rankin Scale (score \leq 1), Glasgow Outcome Scale (score = 1), and the NIHSS (score \leq 1). The results of NINDS-2 confirmed the positive three month outcome results seen