Genentech and Mitsubishi unblock stroke market

On June 18, 1996, the recombinant tissue plasminogen activator Activase (alteplase), developed by Genentech (South San Francisco, CA), became the first drug approved by the US Food and Drug Administration (Rockville, MD) for the treatment of acute ischemic stroke. On the same day, Texas Biotechnology (Houston, TX) announced that its partner, Mitsubishi Chemical (Tokyo, Japan) had obtained approval for Novastan, an L-arginine derivative that inhibits thrombin directly, for the same indication in Japan. Texas Biotechnology is developing the compound for non-stroke indications.

As the first companies with stroke drugs, Genentech and Mitsubishi will forge their own markets, but this may in the end only pave the way for cheaper drugs, including streptokinase.

The efficacy of both Activase and Novastan depends on administering them shortly after the stroke—within three hours in the case of Activase. This narrow timeframe demands radical changes in medical practice, including widespread education of both professionals and the public. The medical establishment may not yet be prepared to treat stroke.

The approval of Activase was based on a trial conducted by the US National Institute of Neurological Disorders and Stroke (Bethesda, MD). Of every 100 patients treated with Activase within 3 hours of the onset of symptoms, at least 11 more than in the placebo group had a favorable outcome—minimal or no disability—at 3 months. The drug did not decrease the mortality rate of stroke patients but neither did it increase it, despite a raised level of hemorrhage in treated patients. Novastan's approval in Japan was based on clinical trial data which indicated that nearly 60% of patients treated with the drug had significant global neurological improvement, compared with 23.7% in the placebo group.

"The key to the success of Activase as a drug is education," says Paul Laland of Genentech. Currently, stroke is not treated as an emergency—simply because there have been no drugs available. Both professionals and the public need to learn not only that stroke is treatable, but that the treatment must be fast.

But education is not itself sufficient. It must herald a change of infrastructure. The Activase trial used very rigorous entry criteria and a protocol that would be almost impossible to reproduce outside of certain very specialized hospitals, according to Peter Sandercock, a reader in neurology at the University of Edinburgh (UK). "Patients must get to hospital, have a CT scan to eliminate brain hemorrhage [as a cause of their symptoms], and be treated with the drug all within three hours." The treatment also requires the presence of specialists to minimize the risk of intracranial bleeding as a result of Activase administration. This may severely limit the use of Activase, at least until more treatment centers recognize the need to upgrade their response to stroke.

The cost of treatment will, of course, be a factor, too. Activase is not cheap—$2200 per dose—and changes in medical practice will probably increase the cost of treatment substantially, although that has yet to be determined definitively. "We haven't finalized the analysis of cost-effectiveness," said Genentech's Laland. Genentech is already funding education programs, in collaboration with the US National Stroke Association (Englewood, CO). There is room to maneuver on cost, though. According to the US National Stroke Association, the average cost of stroke treatment for the first 90 days ranges from $15,000 to $35,000 per patient, and the annual bill for health care for stroke patients in the United States is over $30 billion.

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The advantage for Genentech of being first in the stroke market, of course, is that Activase has no competition. Novastan is not being developed for stroke outside Japan. Texas Biotechnology and Synthelabo (Paris) have rights in the United States and Europe, respectively, but in non-central nervous system (CNS) indications. Novastan is being developed as an adjunct to thrombolytic agents in heart attack and for thrombocytopenia induced by treatment with heparin. It is Genentech, in fact, that owns the rights to develop the drug for CNS disorders, including stroke, in the United States but is not pursuing them.

Several drugs in late-stage development could challenge Activase's position in the next two to three years. They fall into two broad categories: those such as thrombolytic agents and thrombin inhibitors that target the blood clot, and neuroprotectants that target the cascade of molecular events leading to cell death, but which leave the blood clot to dissolve naturally.

Late-stage anticlot drugs include Ancrod from Knoll (Ludwigshaven, Germany), a viper venom-derived anticoagulant and Activase's old rival in heart attack treatment, streptokinase. Ancrod is in phase III trials in the United States, whereas streptokinase, a generic drug produced by a number of companies, has already undergone a number of physician-organized trials in stroke, with new ones about to begin, according to Peter Sandercock.

Pharmacia & Upjohn's (Kalamazoo, MI) Freedox is a neuroprotectant in phase III trials for stroke. It has already received approval in approximately 12 countries for intracranial bleeding. Another neuroprotectant in phase III trials is Cerestat from Cambridge Neuroscience (Cambridge, MA), an NMDA antagonist. Identification of a new class of NMDA receptor antagonists is reported in this issue of *Nature Biotechnology* (see pp. 986–991).

The logistic barrier for neuroprotectants is probably lower than for thrombolytic agents. They can usually be administered before a CT scan and have a wider window of treatment than Activase—six hours for Cerestat, for instance. According to Robert McBurney, chief scientific officer of Cambridge Neuroscience, neuroprotectants could be used in combination with the thrombolytics. In any case, the approval of Activase is good news for Cambridge Neuroscience. "We are pleased about the approval of Activase." explains McBurney. "The trial and education program means that more stroke patients will get to hospital on time to receive Cerestat in our trial."

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