Clinical Trials of Neuroprotective Therapies

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Abstract—There have been numerous failures in the field of acute stroke therapy over many years, but the first large clinical trial showing preliminary indications of efficacy and safety of a neuroprotective drug, NXY-059, has now been fully reported. If confirmed, it will mean that a second therapy for acute stroke has been identified and neuroprotective drug development as a class can proceed. Additionally, a new class of drugs, HMG CoA-reductase inhibitors (statins), specifically high-dose atorvastatin, has been shown to be safe and effective for secondary stroke prevention. This drug should now become a regular part of stroke patient care. (Stroke. 2007;38[part 2]:791-793.)

Key Words: acute Rx ■ acute stroke ■ free radicals ■ prevention ■ statins

After years of some frustration, we have finally had some successful clinical trials for treatment of ischemic strokes. One is the first neuroprotective agent to be shown to be effective when administered after the onset of strokes, and the other is definitive proof that a statin is useful for secondary stroke prevention.

NXY-059 is a free-radical trapping agent. Preclinical animal model development began when the drug was administered starting 3 or 6 hours after 2 hours of middle cerebral artery occlusion in rats. The investigators found that when NXY-059 was administered for 24 or 48 hours at various doses, the drug was effective in reducing lesion volume and neurological deficits, despite the fact that it did not cross the blood-brain barrier to any appreciable extent. Subsequently, marmosets were trained to perform a hand/eye coordination task and then were subjected initially to permanent occlusion of the middle cerebral artery with NXY-059 being started 5 minutes later using an osmotic mini-pump. NXY-059 significantly reduced neurological damage in these primates. In a more stringent test, treatment was delayed for 4 hours. Those animals were treated with the drug for 48 hours using the osmotic mini-pump set to deliver 85 μmol/kg per hour, and the tests were done at 3 and 10 weeks after stroke onset. NXY-059 substantially attenuated neglect at 3 weeks and no deficits were detected at 10 weeks, but there was reduced infarct size compared with saline controls.

For our studies using a rabbit embolic stroke model, we synthesized our own generic NXY-059 which is designated di-S-PBN (or NXY-059G). We evaluated the drug when it was infused at a dose of 100 mg/kg over 30 minutes, 5 minutes or 3 hours after embolization, and the animals were rated 24 hours later. We found that neurological function in 50% of a group of animals (classified using a dichotomous scale as to whether the rabbits were severely neurologically damaged or not) was increased relative to control by 153% when the drug was administered 5 minutes after embolization, but when treatment started at 3 hours, the drug increased neurological function by 193%, which were both statistically significant results. Moreover, when a group of rabbits was treated with tissue plasminogen activator (tPA), 3.3 mg/kg, 60 minutes after embolization and the di-S-PBN therapy was delayed to 3 hours, the combination produced statistically significantly reduced neurological damage, indicating that there was a synergistic effect of the treatment combination.

Additionally, we used a large clot embolic stroke model, which produces intracerebral hemorrhages. We tested the combination of di-S-PBN and tPA. We found that when tPA was administered 60 minutes after embolization and di-S-PBN was given at 5 minutes after the embolization, the combination significantly decreased hemorrhage volume compared with vehicle control or either drug given alone.

These studies were the basis for the clinical development of NXY-059. The animal model studies were used to help identify an optimal blood concentration although the duration of treatment was not fully examined. After 2 phase II studies in which the drug was found to be well tolerated, a dose of 2270 mg for the first hour reduced to 480 to 960 mg/hour with the aim of maintaining a target concentration of 260 μmol/L for a further 71 hours was considered optimal.

To pursue clinical development of NXY-059 for acute stroke, 3 trials were initiated. One, entitled Stroke-Acute Ischemic NXY Treatment I (SAINT I), predominantly conducted in Europe, and a second, SAINT II, in the USA and much of the rest of the world, were begun. These were phase III trials (safety and efficacy). Additionally, a safety trial of this dose of NXY-059 in hemorrhage patients, the Cerebral Hemorrhage and NXY-059 Treatment trial (CHANT), was begun a few months later with the objective of showing that NXY-059 was safe to give to all stroke patients, even without imaging studies before drug administration. For the SAINT I trial, the primary article has been published.
In the SAINT I trial, 1699 patients were randomized to either NXY-059 or placebo if they presented for medical care within 6 hours after symptom onset. If they came into the hospital within 3 hours and were eligible for thrombolysis by standard guidelines, they received either tPA plus NXY-059 or tPA plus placebo. If they were not candidates for tPA, they received NXY-059 alone or placebo. If they presented after 3 hours, they were administered NXY-059 or placebo. An important feature of the trial was that all study sites had to maintain an average time-to-treatment of 4 hours. If their average treatment time rose above this, the 3- to 6-hour time window was closed to them. As a consequence, almost 29% of the patients received tPA, and the average time to NXY-059 treatment was 3 hours 46 minutes. Concerning the primary end point, the Rankin scale was used, and overall, NXY-059 significantly improved the distribution of scores \( (P=0.038) \) compared with placebo. Mortality rates and serious and less serious adverse events were not different between the 2 groups. NXY-059 did not improve the neurological function as measured by the NIHSS (National Institutes of Health Stroke Scale), although this was considered by the investigators to be a secondary end point. Perhaps there is considerable reason to believe that this scale is not as meaningful as the Rankin scale for measuring outcomes of a stroke clinical trial, primarily because the NIHSS is not an ordinal scale whereas the Rankin scale is. There was no interaction between tPA and NXY-059 found in this trial; however, the number of patients was relatively small, and therefore an interaction may have been missed. As predicted by our rabbit study, in this clinical trial, NXY-059 plus tPA was associated with a lower incidence of any hemorrhagic transformation \( (P=0.001) \) and symptomatic intracranial hemorrhage \( (P=0.036) \).

These are extremely important findings because SAINT I implies that we may have finally identified a neuroprotective agent for treatment of stroke. The effect size is relatively modest, with a number-needed-to-treat to get a complete recovery of \( \approx 22 \), and the number-needed-to-treat to get any improvement of around 8. The findings need to be confirmed before most experts in the field will believe that they are true. That is the purpose of the SAINT II trial. Furthermore, the finding that NXY-059 reduces tPA-associated hemorrhages by \( > 50\% \), alone, would justify use of NXY-059.

There is also important news for secondary prevention of ischemic stroke. Until now, the only methods known to prevent strokes have been to control hypertension or reduction of thrombo-embolism with anticoagulants, antiplatelet agents or carotid endarterectomy. HMG CoA-reductase inhibitors (statins) have been tested for years in large trials of patients at risk for cardiac problems, and subanalyses of these studies have usually shown that various statins reduce stroke incidence in the patients who have cardiac disease. This is not surprising because stroke is usually the same disease (atherosclerosis) in a different vascular bed. Based on these findings, the FDA has approved both simvastatin and atorvastatin for stroke prevention. The most relevant of the cardiac studies for evaluating the effects of a statin in stroke prevention is the Heart Protections Study (HPS). Whereas that trial did find stroke would be prevented by use of simvastatin in patients with cardiac risk factors, it failed to show that patients who had experienced a prior stroke or transient ischemic attack (TIA) without prior known cardiac problems would have fewer strokes. However, the patients with prior stroke but without other cardiac disease in the HPS were recruited after a delay of an average of over 4 years, which is well after recurrent strokes or TIs normally occur.

The Stroke Prevention with Aggressive Reduction in Cholesterol Levels (SPARCL) trial evaluated such patients in detail (the protocol has been published\(^1\)). The results of this trial were first released just before the Princeton Conference, at the European Stroke Conference. A total of 4731 patients with stroke or TIA within the prior 6 months and without known coronary artery disease were randomized to placebo or atorvastatin 80 mg/day. The primary end point was the occurrence of recurrent stroke or death after randomization. The patients at the time or randomization also had to have a LDL cholesterol level in the normal to moderately elevated range of between 100 and 190 mg/dL.

The patients were followed for an average of almost 5 years. There was considerable difficulty with patients leaving the study (dropouts) and others who started taking statins (of various types and at variable doses and lengths of time) outside of the study (dropins). Between the 2, by the end of this long study, over 22% of the subjects were protocol violators. Therefore, the actual effects (per protocol) of atorvastatin are probably underestimated. One month after randomization, the total cholesterol for the group taking atorvastatin had decreased to 147 mg/dL, whereas it remained at 208 for the placebo group. The mean LDL cholesterol was 73 mg/dL during treatment with atorvastatin and 129 during treatment on placebo. A primary end point occurred in 265 patients in the atorvastatin group compared with 311 in the placebo group; therefore, the absolute difference at 5 years was 2.2% \( (P = 0.05) \). After adjustment for prespecified baseline factors, the \( P \) value was 0.03. Despite the fact that patients with known coronary heart disease were excluded at baseline, analysis of secondary end points demonstrated that there were reductions in combined risk of major cardiovascular events \( (334 \text{versus} 407, P = 0.005) \). Therefore, stroke or TIA should be considered a coronary heart disease risk. There was no difference in all-causes mortality.

Despite the fact that all types of strokes and TIs were decreased, there was an increase in the frequency of brain hemorrhages; 55 were in the atorvastatin group and 33 in the placebo group. However, the occurrence of fatal hemorrhagic stroke did not differ between the 2 treatment groups. The reasons for this increase in brain hemorrhages are not clear at this time. Safety assessments revealed no significant differences in serious adverse events aside from hemorrhages, and in particular, there were a total of 5 cases of rhabdomyolysis: 2 in the atorvastatin group and 3 in the placebo group. Before the study there was considerable concern that rhabdomyolysis would be a problem.

It should be expected that statin therapy will become a standard of care for secondary prevention of stroke. Whether other statins beside atorvastatin are effective is not known at this time.
The past year has begun a hopeful period for stroke therapy. A new class of drugs for prophylaxis has now been proven to be effective. The effect size was small, but the result is unequivocal, and the side effects, excepting a small risk of intracerebral hemorrhage, appear to be minimal. The magnitude of the effect is similar to aspirin, the current drug of choice for secondary stroke prevention, although there is every reason to expect that patients will be treated with both classes of drugs and antithrombotics.

Concerning acute treatment, the first neuroprotective has been shown to be effective in a large clinical trial. Again, the effect size is small, but side effects are essentially nonexistent. There are 3 landmark implications of this effort. First, it has finally been proven that a drug that primarily acts by protecting nervous tissue (instead of restoring blood flow) is effective. Decades of effort have gone into developing such drugs without previous clinical success. Second, a treatment has been found that appears to reduce tPA-induced hemorrhages. Many emergency room physicians and neurologists have identified the risk of hemorrhages as a principal reason for their avoidance of use of tPA therapy—at present only ~4% of stroke victims in the US are receiving this treatment. If this hypothesis is correct, the use of a very safe drug (NXY-059) in addition to tPA should increase the popularity of thrombolytic therapy. Finally, if the SAINT II trial confirms the SAINT I results, the success of the first neuroprotective therapy will validate the methods that were used in these trials. Improvements in the way the trial was conducted (closer to the findings in preclinical studies) and methods of data analysis are probably important factors in this success. It is probable that many of the neuroprotective agents that failed in previous trials would actually have been proven to be effective if the newer clinical investigation techniques had been used. Foremost among these is the fact that the SAINT I trial recruited patients at an average of <4 hours after symptom onset. In virtually all of the previous trials, use of a 6-hour time window for initiation of therapy meant that the average time-to-treatment was over 5 hours. Time is brain. Hopefully, discovery of a new stroke prophylactic class of drugs and a neuroprotective for acute stroke therapy that both have modest effects will encourage other pharmaceutical manufacturers and biotechnology companies to once again enter the stroke therapy arena, and even more effective treatments will be identified.

Disclosures
Dr Zivin has in recent years received consultant fees from both AstraZeneca (NXY-059) and Pfizer (atorvastatin) for helping to run their trials. The dollar amounts in both cases (in aggregate) exceeded $10,000.

Addendum
A few months after the Princeton Conference, the preliminary results of the SAINT II trial (which was nearly twice the size of SAINT I) became available. Unfortunately, that trial did not confirm a difference between NXY-059-treated and control patients. Therefore, development of NXY-059 for stroke has now terminated. The results of the 2 trials are in conflict, and it will not be possible to fully decide which one produced inaccurate results. All of this is particularly regrettable because it is likely that major drug manufacturers will abandon the field of neuroprotection for acute stroke for the foreseeable future. The fact that 1 large trial was positive suggests that the methodology for identification of such drugs has improved but not enough to be reliable at present.

References
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