Thrombolytic Agent/Glycoprotein IIb/IIIa Receptor Blocker Combination Therapy for Middle Cerebral Artery Occlusion

**Speaker:** George Gahn, MD, Professor, Department of Neurology, University of Technology, Dresden, Germany.

Therapy combining systemic recombinant tissue plasminogen activator (rt-PA) (Activase®, Genentech), a well-known thrombolytic agent, and abciximab (ReoPro®, Eli Lilly), a glycoprotein (GP) IIb/IIIa platelet receptor blocker, is a safe and effective treatment for patients with stroke caused by occlusion of the middle cerebral artery (MCA). Compared with rt-PA alone, the combination approach achieves a higher rate of recanalization (a procedure in which the patency of an occluded vessel is restored).

MCA occlusion was prospectively monitored in 27 patients by repeated transcranial color-coded duplex sonography within 24 hours of thrombolysis. Patients were eligible for thrombolysis if they fulfilled clinical and computed tomography (CT) criteria and MCA occlusion confirmed by CT angiography. The first 16 patients (group A) received rt-PA at a dose of 0.9 mg/kg alone; the next 11 patients (group B) were given rt-PA at a dose of 0.45 mg/kg combined with abciximab 0.125 mcg/kg per minute.

In group A, 50% of patients (8 of 16) experienced recanalization; in group B, 91% of patients (10 of 22) did so. All patients with reopened arteries in group A had favorable outcomes, and their modified Rankin Scale (MRS) scores ranged from 0 to 2. The MRS scores of the other eight patients ranged from 4 to 6, and the outcomes for the remaining patients were poor.

In group B, all 10 patients with reopened arteries had favorable outcomes; five patients achieved MRS scores of 0 to 2, and five patients had scores of 3 to 5. It is interesting that the group B patients with persistent MCA occlusion regained 1 point on the MRS.

Selective Thrombin Inhibitor for All Types of Acute Stroke

**Speaker:** Kuniyasu Wada, MD, Neurologist, Cerebrovascular Division, Graduate School of Medical Sciences, Kumamoto University, Kumamoto, Japan.

Argatroban Injection (GlaxoSmithKline), a synthetic direct thrombin inhibitor, is indicated in the U.S. as an anticoagulant for patients at risk of heparin-induced thrombocytopenia. It has the potential to be effective for acute ischemic stroke, regardless of the subtype.

Argatroban was approved in Japan in 1996 for the treatment of ischemic stroke. To determine whether it would be safe and effective for each subtype, researchers analyzed data from 3,016 ischemic stroke patients who were admitted to 30 centers in the Japan Standard Stroke Registry Study. The main criterion for entrance into the study was admission to a hospital within 48 hours of stroke onset.

Ischemic stroke subtypes and National Institutes of Health Stroke Scale (NIHSS) scores on admission and at discharge were documented for the 655 patients who received Argatroban. Changes in NIHSS scores were used to assess the agent’s effects.

Argatroban was administered continuously as an intravenous (IV) infusion at 60 mcg/kg per minute for the initial two days, followed by a 10-mg injection every 12 hours for five days.

Ischemic stroke subtypes found after Argatroban therapy included atherothrombotic brain infarction (ATBI) in 321 patients, artery-to-artery embolism (ATAE) in 47, cardioembolic infarction of the brain (CEBI) in 122, lacunar infarction (LI) in 134, and other forms of ischemic stroke in 31.

The changes in NIHSS scores were –1.4 ± 0.5 in patients with ATBI, –1.1 ± 1.5 in those with ATAE, –1.6 ± 0.9 in those with CEBI, and –2.0 ± 0.3 in those with LI. Overall, no significant differences were seen in the efficacy of Argatroban among any of the stroke subtypes.

The incidence of bleeding was 6.5% in patients with ATBI, 8.6% in those with ATAE, 14.1% in those with CEBI, and 1.0% in those with LI, suggesting that the risk of bleeding in patients with embolic stroke, particularly CEBI, is considerable.
Low-Dose Thrombolysis for Ischemic Stroke After Three Hours of Onset

Speaker: Ken Uchino, MD, Cerebrovascular Fellow, University of Texas Stroke Treatment Team, University of Texas–Health Science Center at Houston Medical School, Houston, Texas.

Low-dose IV rt-PA (Activase®, Genentech) in a dose of 0.5 mg/kg for patients with ischemic stroke after three hours from onset carries some risk, but considering the severity of strokes in this study, hemorrhage and mortality rates were acceptable and recanalization with dramatic recovery was sometimes possible.

A prospective study of low-dose rt-PA in stroke patients who were examined after the first three hours from symptom onset was performed to assess the safety of this approach. Eligible patients received IV rt-PA 0.6 mg/kg, up to 60 mg, 15% as a bolus, and 85% as an infusion over 30 minutes. Thirty patients were treated within the protocol, with a median age of 70 years; their median baseline NIH Stroke Scale (NIHSS) score was 19 (range, 7–34). The rt-PA bolus was administered at a median of approximately 5.3 hours after stroke onset.

Of 23 patients who were continuously monitored by transcranial Doppler imaging, seven patients experienced complete recanalization within one hour after the rt-PA bolus. Symptomatic hemorrhage occurred in three of the 30 treated patients, including one who experienced fatal bleeding. Overall, six of the 30 patients died, for a mortality rate of 30%. Four of the 30 patients (13%) experienced early major improvement.

Astrocyte Activation Modulator for Acute Stroke

Speaker: L. Creed Pettigrew, MD, Professor of Neurology, University of Kentucky College of Medicine, Lexington, Kentucky.

Arundic acid (ONO-2506) (Ono Pharma USA, Inc.), an investigational agent that modulates the astrocyte-derived protein S-100 beta, which augments ischemic neuronal degeneration, appears to be safe for patients with acute ischemic stroke and shows promising trends in stroke outcomes.

A multicenter, phase I study of this novel modulator of astrocyte activation included acute ischemic stroke patients. S-100 beta was used as a surrogate marker of clinical efficacy. Serum levels of S-100 beta were obtained periodically from all patients and were correlated with the NIHSS which quantifies neurological deficits. The goals of this study were (1) to establish whether S-100 beta correlated with NIHSS scores within seven days of an acute ischemic stroke and (2) to determine the effects of arundic acid on S-100 beta and NIHSS scores.

The study was carried out at 18 U.S. medical centers. Ninety-two patients with a confirmed acute ischemic stroke were randomly selected to receive arundic acid or a matching placebo for a two-hour infusion every 24 hours until they received seven doses. The patients were randomly selected to receive doses of 2, 4, 6, 8, 10, or 12 mg/kg per hour, with 12 to 16 patients in each group. After each dose tier was completed, enrollment was halted temporarily; an external data safety monitoring board reviewed the safety data before enrollment was resumed for the next tier. Follow-up treatment continued until 40 days of therapy had begun.

A complete set of S-100 beta samples was obtained from 86 patients. Pooled S-100 beta data from the 40 placebo-treated patients clearly revealed that serum S-100 protein levels did not change immediately but became elevated 48 to 72 hours later. They reached a peak at 0.0582 ng/ml at three hours after the infusion on the third day following initiation of the study medication. After this peak was reached, the serum S-100 beta levels declined, returning to baseline values by the end of the seventh day. The average change in S-100 levels from one day before infusion to three days after infusion was significantly lower in patients receiving arundic acid doses of 2, 8, and 10 mg/kg per hour than in patients receiving placebo. The active drug was most useful three to six hours after infarction. Dose-related responses, however, could be estimated at the tested range of 2 to 12 mg/kg per hour.

New Investigational Agent for Acute Ischemic Stroke

Speaker: Phillip Teal, MD, Division of Neurology, Department of Medicine, and Brain Research Centre, University of British Columbia, British Columbia, Vancouver, Canada.

Intravenous (IV) administration of the investigational agent repinotan (Bayer Pharmaceuticals) in patients with acute ischemic stroke has had positive pharmacological effects, with higher success rates than those of placebo.

To evaluate the effect on outcomes and the pharmacokinetics of IV repinotan in the treatment of acute ischemic stroke, investigators enrolled 240 patients in a phase II, multicenter, randomized, double-blind, placebo-controlled study. The patients were randomly selected to receive IV repinotan at doses of 0.5, 1.25, or 2.5 mg/day or placebo for 72 hours, initiated no later than six hours after the onset of stroke symptoms. The NIHSS, the Barthel Index (BI), and the modified Rankin Scale (MRS) were used to evaluate success rates at four weeks and at three months. Plasma repinotan levels were measured to determine any correlation with successful outcomes.

Overall, success rates were numerically higher for patients receiving repinotan 0.5 mg/day and 1.25 mg/day. Subgroup analyses showed that patients with baseline NIHSS scores of 8 to 25 fared better with repinotan than with placebo. Plasma repinotan levels ranging from 5 to 20 mcg/L were associated with the greatest chance of success. Repinotan 1.25 mg/day was the most effective of the doses studied to achieve this range.

Amphetamine plus Physiotherapy for Acute Stroke

Speaker: David J. Gladstone, MD, Assistant Professor of Medicine (Neurology), University of Toronto; Director, Inpatient Stroke Services; and Co-Director, Stroke Prevention Clinic, Sunnybrook & Women’s College Health Sciences Centre, Toronto, Ontario, Canada.

The addition of dextroamphetamine (Dexedrine®, Glaxo-SmithKline; Aderal®, Shire; dextroamphetamine sulfate, Mallinckrodt) to physiotherapy for motor rehabilitation in patients with moderate-severity hemiparesis after an acute
stroke may accelerate motor recovery, although the drug adds little to physiotherapy alone in the early post-recovery period in stroke patients with severe motor deficits.

Because the clinical efficacy of this agent in human stroke rehabilitation is unknown, 71 stroke patients were enrolled into a randomized, double-blind, placebo-controlled trial from 2000 to 2003. Hemiparesis was classified as moderate to severe.

Patients were randomly assigned to 10 sessions of physiotherapy with either dextroamphetamine 10 mg or placebo in addition to standard care. The treatments were given by a single physiotherapist to all participants and began five to 10 days after the stroke and continued twice weekly for five weeks. The primary endpoint was motor recovery at the impairment level as measured by the Fugl-Meyer Assessment (FMA) (range, 0–100).

Overall, baseline hemiparesis was severe, with a mean FMA motor score of 28 ± 20. During treatment, scores improved in both groups, with a mean FMA motor score change of 25 ± 15. For the entire study population as a whole and for the 44 patients with severe hemiparesis, there was no difference in recovery between those who received dextroamphetamine or placebo. In the moderate-severity subgroup, however, patients receiving the addition of dextroamphetamine to physiotherapy experienced significantly greater upper-extremity motor recovery than did patients receiving placebo, with mean gains in FMA scores of 29 ± 12 for the treated patients versus 17 ± 9 for placebo patients, respectively.

Statins for Nonlacunar Infarction of the Brain
Speaker: Rafael Merino, MD, Consultant Neurologist, La Paz University Hospital, Madrid, Spain.

Retrospective results from a sequential five-year study of patients demonstrated that previous treatment with statins results in good outcomes in patients with a nonlacunar brain infarction. Because an earlier study had suggested that previous treatment with statins might be associated with better outcomes in ischemic stroke patients, the researchers decided to assess the possible influence of previous statin treatment in patients with a nonlacunar infarction.

An observational study of sequential patients in the stroke unit registry was carried out from 1998 to 2002. Patients were classified into two groups according to whether or not they had received statins earlier. The modified Rankin Scale (MRS) was used to determine their outcomes at discharge from the hospital. A score of 3 to 6 was considered to be related to poor outcomes. Statistical tests included univariate analyses and a multivariate logistic regression model.

Of the 2,231 patients with ischemic stroke during the five-year period, 985 had a nonlacunar infarction in the brain. Of these patients, 5% were receiving statin treatment. Univariate analyses indicated that treatment with statins was associated with better outcomes at hospital discharge. The multivariate logistic regression model confirmed that previous statin treatment was an independent predictive factor for good outcomes in patients with nonlacunar infarctions of the brain.

Recombinant Blood Factor for Warfarin Anticoagulation Intracranial Hemorrhage
Speaker: James F. Meschia, MD, Staff Neurologist, Mayo Clinic, Jacksonville, Florida.

Results from a retrospective case study series suggest that IV bolus administration of recombinant factor VIIa (rFVIIa) (NovoSeven®, Novo Nordisk Pharmaceuticals), a relatively new drug, rapidly corrects warfarin sodium (Coumadin®, Bristol-Myers Squibb) anticoagulation in patients with intracranial hemorrhage (ICH), but patients should also receive vitamin K and/or fresh frozen plasma to ensure full and lasting reversal of damage. Although warfarin is generally administered to patients with atrial fibrillation, ICH is often a medical emergency requiring rapid reversal to prevent hematoma growth and to facilitate surgical removal.

A retrospective study was conducted to review the clinical, laboratory, and radiographic features of a consecutive series of seven patients with acute, nontraumatic, warfarin-related, symptomatic ICH who had received rFVIIa. The MRS was used to assess patients’ pre-stroke baseline functional status, and the Glasgow Outcome Scale (GOS) was used to evaluate their status at discharge. Hematoma volumes were also measured. All patients had been prescribed warfarin for atrial fibrillation. The median pre-stroke MRS score was 0, and the median GOS score was 3.

rFVIIa was administered as a 5- to 10-minute IV injection at a mean dose of 55.8 mcg/kg. A mean dose of 10.4 mg of vitamin K and a mean dose of 6 units of fresh frozen plasma were also administered. (The customary approach for reversing anticoagulation involves only fresh frozen plasma and blood products and generally takes hours.)

The mean International Normalized Ratio (INR) was 2.7. The initial post-rFVIIa drop in INR values was 0.6, measured at 0.8 hours after initiation of therapy, 0.8 at 7.5 hours, 1.0 at 1.9 hours, 1.3 at 1.6 hours, 1.4 at 2 hours, and 2.4 at 1.3 hours, respectively. Overall, the patients seemed to function better than what would typically be expected after an ICH. Four of the seven patients survived and were discharged from the hospital.