Argatroban tPA Stroke Study

Study Design and Results in the First Treated Cohort

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Background: The benefit of intravenous recombinant tissue plasminogen activator (rtPA) in acute stroke is linked to clot lysis and artery recanalization. Argatroban is a direct thrombin inhibitor that safely augments the benefit of rtPA in animal stroke models. There are no human data on this combination.

Design: We report the first phase of the Argatroban tPA Stroke Study, an ongoing prospective, open-label, dose-escalation, safety and activity study of argatroban and rtPA in patients with ischemic stroke. The primary outcome was incidence of intracerebral hemorrhage; secondary outcome, complete recanalization at 2 hours. After standard-dose intravenous rtPA administration, a 100-µg/kg bolus of argatroban followed by infusion of 1 µg/kg per minute for 48 hours was adjusted to a target partial thromboplastin time of 1.75 times that of the control group.

Results: Fifteen patients (including 10 men) were enrolled, with a mean±SD age of 61±13 years. All patients had middle cerebral artery occlusions. Baseline median National Institute of Health Stroke Scale score was 14 (range, 4-25). The mean±SD time from symptom onset to argatroban bolus administration was 172±53 minutes. Symptomatic intracerebral hemorrhage occurred in 2 patients, including 1 with parenchymal hemorrhage type 2. Asymptomatic bleeding occurred in 1 patient and there was 1 death. Recanalization was complete in 6 patients and partial in another 4, and reocclusion occurred in 3 within 2 hours of rtPA bolus administration.

Conclusion: The safety of low-dose argatroban combined with intravenous rtPA may be within acceptable limits, and its efficacy for producing fast and complete recanalization is promising, but a larger cohort of patients is required to confirm these preliminary observations.

Trial Registration: clinicaltrials.gov Identifier: NCT00268762

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Argatroban (GlaxoSmithKline, Philadelphia, Pa) directly and selectively inhibits the action of free and clot-associated thrombin.1-3 Argatroban is approved for treatment of heparin-induced thrombocytopenia. It is safe alone or in combination with thrombolitics or aspirin in patients with acute myocardial infarction.4-7 In animal stroke models, argatroban safely augments the benefit of recombinant tissue plasminogen activator (rtPA) by improving flow in the microcirculation, increasing the speed and completeness of recanalization, and preventing reoclusion.8-11 Kobayashi and Tazaki13 gave argatroban to 60 patients within 48 hours of stroke onset and found a significant improvement in neurological outcome compared with placebo. The Argatroban Anticoagulation in Patients With Acute Ischemic Stroke (ARGIS-1) Study showed that argatroban given within 12 hours of ischemic stroke provides safe anticoagulation without an increase in intracerebral hemorrhage (ICH).14 However, no clinical benefit was observed.

Intravenous (IV) rtPA in acute stroke patients has limitations in efficacy and application. Fifty-seven percent of the patients in the National Institute of Neurological Disorders and Stroke (NINDS) rt-PA Stroke Study and 58% in the Second European-Australasian Cooperative Acute Stroke Study (ECASS-II) did not show a favorable clinical response.15-17 The benefit of rtPA in acute stroke is linked to the speed and degree of clot lysis and artery recanalization.18-20 However, only 20% to 30% of patients will have complete recanalization on transcranial Doppler imaging (TCD).
within 2 hours of IV rtPA therapy, as many as 60% will have only partial recanalization, and 34% of those with any recanalization will experience reocclusion.\textsuperscript{21,22}

Because of its short half-life, allowing careful titration of the anticoagulant effect, we hypothesized that argatroban might be safely added to full-dose IV rtPA. We also hypothesized that the addition of argatroban to rtPA would increase recanalization rates and therefore increase benefit. We report the prespecified first phase of a prospective single-arm, dose-escalation, safety and activity study evaluating the rate of bleeding and successful recanalization with combined rtPA and argatroban administration in acute ischemic stroke.

METHODS

OBJECTIVES

The primary objective of this study was to assess the safety of combined argatroban and rtPA treatment in an ischemic stroke population as measured by the incidence of ICH. Symptomatic hemorrhage was defined as ICH present on cerebral computed tomography (CT) temporally related to a decline in neurological status and consistent with new or worsening symptoms in the judgment of the clinical investigator. We defined parenchymal hemorrhage type 2 (PH-2) as confluent bleeding occupying more than 30% of the infarct volume and causing significant mass effect.\textsuperscript{23} The secondary objectives of this study were to evaluate drug activity by determining the speed and completeness of arterial recanalization and reocclusion on TCD. We prospectively planned to compare our results with those of a control cohort from the previously reported Combined Lytic Strokes in Baseline Ultrasound and Systemic tPA (CLOTBUST) trial.\textsuperscript{24} This control cohort received rtPA alone and underwent the same selection criteria and TCD monitoring of activity and safety as the patients in this trial.\textsuperscript{25}

PATIENTS

Inclusion criteria were (1) men and nonpregnant women aged 18 to 85 years; (2) ischemic stroke symptoms with onset within the past 3 hours; (3) a clot causing complete or partial occlusion (Thrombolysis in Brain Ischemia [TIBI] flow grades of 0, 1, 2, or 3) identified by TCD before argatroban infusion in the middle cerebral artery (MCA) M1 (45- to 65-mm depth) or M2 (<45-mm depth of worst TIBI signals on TCD findings) segment; and (4) being eligible by National Institute of Neurological and Communication Disorders and Stroke criteria for IV rtPA treatment.

Exclusion criteria were (1) National Institutes of Health Stroke Scale (NIHSS) level-of-consciousness score of 2 or more; (2) baseline NIHSS total score less than 5 or rapidly resolving deficit consistent with a transient ischemic attack; (3) baseline NIHSS total score of greater than 17 (modified to >15) for right hemisphere strokes and greater than 22 (modified to >20) for left hemisphere strokes; (4) preexisting disability with modified Rankin Scale score of 2 or more; (5) ICH or significant bleeding episode within the past 3 months; (6) stroke, myocardial infarction, pericarditis, intracranial surgery, or significant head trauma within 3 months; (7) alcohol or other substance abuse; (8) life expectancy of less than 3 months; (9) need for concomitant use of anticoagulants other than argatroban; and (10) participation in any investigational drug or device study within the past 30 days.

TREATMENT AND EVALUATION

All patients underwent initial evaluation and management by the same experienced stroke team. Written informed consent was obtained from all patients or their legal representatives. Before starting argatroban treatment, all patients had blood drawn for complete blood cell count with differential and platelet counts and underwent measurement of activated partial thromboplastin time (aPTT), prothrombin time, and international normalized ratio, analysis of electrolyte and liver function panels, urinalysis, measurement of serum $\beta$ human chorionic gonadotropin level (in women), electrocardiography, noncontrasted brain CT, TCD, and evaluation of NIHSS and modified Rankin Scale score. All patients were admitted to the neurology/neurosurgery intensive care unit or the intermediate care stroke unit.

All patients received the standard rtPA dose of 0.9 mg/kg, with 10% of the total dose given in 1 minute and the remainder infused across 60 minutes. For the first tier of 15 patients described herein (phase 1), argatroban was administered intravenously within 1 hour of rtPA treatment initiation as an initial 100-$\mu$g/kg bolus in 3 to 5 minutes, followed by a continuous infusion of 1.0 $\mu$g/kg per minute for 48 hours adjusted to a mean $\pm$5D target aPTT of 1.75 times baseline ($\pm$10%). We developed a dosing algorithm so that standardized increments or decrements of argatroban infusion rate took place in response to the aPTT. The aPTT was monitored at baseline and 2, 6, 12, and 24 hours after initiation of argatroban infusion; at the end of argatroban infusion; within 2 to 4 hours of any adjustment in the argatroban infusion; and in the event of a major bleed. Argatroban infusion was terminated immediately if major bleeding or symptomatic ICH was suspected. Major bleeding was defined as any overt bleeding associated with a fall in the hemoglobin level of 2 g/dL or more, requiring a blood transfusion. The start of IV rtPA treatment was not delayed in any patient for participation in this trial. Concomitant administration of other defibrinogenating agents, heparinoids, platelet glycoprotein IIb/IIIa inhibitors, other direct thrombin inhibitors, other thrombolytic agents, dextran, other anticoagulants, and antiplatelet agents was not permitted.

Cerebral CT was performed at initial presentation, 48 hours after the rtPA bolus administration, and at any neurological deterioration associated with an increase in the NIHSS score of 2 points more than baseline. The CT findings were interpreted by a radiologist who was unaware of argatroban treatment. The NIHSS score was measured at 2, 24, and 48 hours after rtPA bolus administration and any time of neurological deterioration. We obtained a modified Rankin Scale score, Barthel index, and Glasgow Outcome Score at 48 hours and 7 days after rtPA bolus administration.

Monitoring with TCD was initiated before administration of the rtPA bolus, at the start of argatroban infusion, and at 30, 60, 90, and 120 minutes and 24 and 48 hours after rtPA bolus administration. Signals from the proximal, middle, and distal portions of the MCA were recorded. For the purposes of this analysis, the proximal and middle portions were considered to represent the M1 segment of the MCA, and the distal portion the M2 segment. Arterial recanalization was determined with the use of the previously validated TIBI system.\textsuperscript{2,13} Recanalization and reocclusion were determined from data using the most proximal portion of the MCA with the lowest qualifying TIBI score. Exceptions were that if flow was absent in a segment, the segment immediately proximal to it was used. If the flow grade was 3 in all segments, the most distal segment was used. Recanalization was defined as an increase in TIBI flow by 1 grade or more compared with baseline and an overall TIBI grade of 2 or more. Partial recanalization was defined as improvement of
flow to grade 2 or 3. Complete recanalization was defined as improvement of flow to grade 4 or 5. Reocclusion was defined as a worsening of TIBI flow signals by 1 grade or more in sequential measurements (whether or not recanalization had occurred), with the following exceptions: TIBI grade 2 or 3 had to result in the disappearance of diastolic flow where it was previously present, ie, nonpulsatile flow (TIBI grade 0 or 1), and TIBI grade 4 or 5 had to decrease to a TIBI grade of 3 or less. A blinded central reader from the University of Texas–Houston Stroke Team (R.M. or Z.G.) interpreted all TCD waveforms.

SAFETY MONITORING

This study was approved by the University of Texas–Houston Committee for the Protection of Human Subjects. An independent data and safety monitoring committee provided safety oversight. Two neurologists unaffiliated with the study in any way reviewed the clinical record, case report forms, and CT findings of each patient. A prospective stopping rule was that enrollment would have been terminated if more than 2 symptomatic hemorrhages or PH-2 events occurred at any time during the enrollment of the first 15 patients.

STATISTICAL ANALYSIS AND BLINDING

This was an open-label, noncontrolled study. Because this was designed to be the first ever exposure of patients with acute stroke to the combination of rtPA and argatroban, a prespecified group size of 15 patients was to be treated in phase 1 to obtain a preliminary assessment of safety, and that group is the subject of this report. When designing this study, we prospectively intended to compare our results with those of the control cohort from our previously reported CLOTBUST trial as a historical comparison group. We used χ², Fisher exact, and unpaired t tests and analysis of confidence (Stata statistical software; StataCorp, College Station, Tex) to compare data within and between cohorts. A P<.05 was considered statistically significant. All values are presented as mean ± SD or median.

RESULTS

From May 1, 2003, through December 31, 2004, 15 patients (including 10 men) were enrolled, with a mean age of 61±13 (median age, 60; range, 44-81) years. All patients had MCA occlusions, including 50% in the M1 and 50% in the M2 segments, 53% in the left hemisphere, and 47% in the right hemisphere. The median baseline NIHSS score was 14 (range, 3-25) points, with 60% having a score of 10 points or more (Table 1). Time from symptom onset to rtPA bolus administration averaged 118±51 minutes. All patients had initiation of argatroban treatment before completion of the rtPA infusion. Fourteen patients received the intended argatroban dose. One patient received only the argatroban bolus without the infusion, secondary to suspected hemorrhagic transformation, which was later not confirmed. The average time to argatroban bolus was 172±53 (median, 156; range, 100-249) minutes. The average time to target aPTT was 472±211 (median, 423; range, 180-994) minutes; however, 9 (64%) of 14 patients had reached or exceeded the target range within 2 hours.

Symptomatic hemorrhage occurred in 2 (13%) of 15 patients (95% confidence interval, 4%-48%). Treatment in 1 of these patients involved a protocol violation owing to a high baseline NIHSS score of 21 with right-hemisphere MCA stroke. Despite the hemorrhage, his NIHSS score decreased to 16 at 7 days. In response to this patient’s hemorrhage, on the recommendation of the data and safety monitoring board, the upper limit of the NIHSS score was reduced to 15 (right hemisphere) and 20 (left hemisphere) after the 10th patient was enrolled. The other patient with symptomatic hemorrhage also had PH-2 and a 7-day NIHSS score (15) that was unchanged from initial presentation (PH-2 inci-

Table 1. Clinical Data for All 15 Patients*

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<th>Patient No./Sex/Age, y</th>
<th>Race or Ethnicity</th>
<th>Hemisphere</th>
<th>NIHSS Score Before Argatroban Treatment</th>
<th>7-Day NIHSS Score</th>
<th>mRS*</th>
<th>Sympt ICH</th>
<th>PH-2</th>
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Abbreviations: Asympt, asymptomatic; ICH, intracerebral hemorrhage; L, left; mRS, modified Rankin Scale score; N, no; NIHSS, National Institutes of Health Stroke Scale; PH-2, parenchymal hemorrhage type 2; R, right; Sympt, symptomatic; Y, yes.

*At 7 days.
†Patient 3 had cerebral edema.

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One patient experienced asymptomatic hemorrhage. One death resulted due to malignant cerebral edema in a patient. At 7 days, the median NIHSS score was 3.5 (range, 0-16) points; median modified Rankin Scale score was 1.5 (range, 0-6); and median Glasgow Outcome Score was 4 (range, 3-5). There was a mean decrease (improvement) in NIHSS scores at day 7 by 5.8±4.3 points (P = .001), but 3 patients did not have all per-protocol follow-up measures.

Monitoring of recanalization with TCD was performed for the 14 patients who received the continuous argatroban infusion (Table 2). Of these, 3, 6, 8, 10, 14, and 14 patients achieved any recanalization at 30, 60, 90, and 120 minutes and 24 and 48 hours, respectively. Complete recanalization occurred in 1, 3, 5, 6, 12, and 12 patients at the same time intervals, respectively. Reocclusion occurred in 3 of 14 patients; 1 patient with early reocclusion had subsequent recanalization (patient 2).

Our results were compared with those from the CLOTBUST control group (n=63) (Figure). Patient demographic characteristics were similar, but not identical, with 7 (50%) of 14 patients with M1- and 7 (50%) with M2-segment occlusion vs CLOTBUST findings of 44 (70%) of 63 patients with M1- and 19 (30%) with M2-segment occlusion (P = .15). The baseline NIHSS median score was 14 (range, 4-25; n=10 in 9 [60%] of 15 patients) compared with the CLOTBUST control median score of 17 (range, 5-29; n=10 in 52 [83%] of 63) (P = .8). The time from symptom onset to rtPA bolus administration was also similar, with a mean of 118±51 minutes in the present study vs 137±32 minutes in the CLOTBUST controls (P = .8). Parenchymal hemorrhage type 2 occurred in 1 (6%) of 15 patients in the present study vs 3 (5%) of the 63 CLOTBUST controls, and symptomatic ICH occurred in 2 (13%) of 15 patients in the present study vs 3 (5%) of the 63 CLOTBUST controls. Recanalization rates by 2 hours after treatment occurred in 10 (71%) of 14 patients in our study and was complete in 6 (43%), vs 24 (38%) and 11 (17%), respectively, of the 63 CLOTBUST controls. Two-hour reocclusion rates were 21% (3 of 14 patients in our study) vs 22% (14 of 63 CLOTBUST controls).

**COMMENT**

This preliminary study highlights the potential hazards and possible benefits of argatroban therapy used in combination with rtPA in patients with acute stroke.

We chose to study argatroban because of its multiple possible actions of increasing the speed and completeness of recanalization while improving flow in the microcirculation\(^1\) and because of its safety in combination with rtPA in experimental models\(^1\) and clinical cardiac trials.\(^2,3\) An advantage of argatroban compared
with some other thrombin inhibitors is its short half-life, which allows rapid offset of action in case of bleeding, and the ease of monitoring its antithrombotic effect by means of the aPTT. Platelet glycoprotein IIb/IIIa antagonists or other antithrombotic agents such as heparin might also be used advantageously in combination with rtPA. None of these agents, including argatroban, have been shown to be useful when given as monotherapy in patients with acute stroke. Therefore, argatroban makes as much sense as or more sense than any other agent to combine with rtPA. We chose the argatroban dose based on 2 considerations. We wanted to give standard-dose rtPA so that patients would not be deprived of proven effective therapy. We started with a low dose of argatroban that had been shown in previous trials to be safe and to only moderately prolong the aPTT. If further study of more patients results in unacceptable bleeding, 1 option would be to lower the dose of rtPA or to target the aPTT prolongation to 1.5 times that of the control aPTT.

The rate of symptomatic ICH in this small study was approximately 2 to 3 times greater than that of a comparable cohort of patients and historical data from the NINDS rt-PA Stroke Study, occurring at the maximum allowable rate before termination for a safety hazard was required. However, one of these was in a patient with a severe stroke who improved, despite the bleeding. Nevertheless, because the NIHSS score is a well-established predictor of bleeding risk in patients receiving rtPA, this led us to put a lower ceiling (NIHSS score of 15 for the right hemisphere and of 20 for the left) on the admission NIHSS score in subsequent patients. No bleeding occurred in patients with NIHSS scores below these limits. Furthermore, only 1 PH-2, which is probably a more objective measure of bleeding risk, occurred. This rate was not significantly different from that of the control patients treated with rtPA and ultrasonography in the CLOTBUST group. Because of the small sample size, the 95% confidence interval for symptomatic ICH was 4% to 48%; for PH-2, 1% to 44%. To be 90% certain that the true PH-2 rate is less than 10%, we would need to enroll another 50 patients. This second phase is ongoing.

Our results can be compared with those of the control cohort of the previously reported CLOTBUST trial. Our study and the CLOTBUST trial share the same patient selection criteria and protocols for monitoring recanalization and safety, thereby providing us with a cohort of patients treated with rtPA only as a comparison group. As expected, we had similar patient populations; however, the argatroban cohort had a higher percentage of M2-segment occlusions. This difference in occlusion site could contribute to recanalization outcome because larger vessel occlusions are known to be more resistant to thrombolytic treatment. Furthermore, the strokes in the argatroban-treated patients were slightly less severe and were treated with rtPA slightly quicker than in the CLOTBUST study, introducing additional bias in favor of argatroban. Although not significant, our results showed a trend toward improved recanalization rates of 71% compared with 38% with rtPA alone. Furthermore, we found complete recanalization rates at 2 hours in 43% vs 17% of patients with rtPA alone. Although these differences are not significant, this trend, if real, could be clinically important. This will also require a larger patient cohort to confirm.

We found no significant difference in reocclusion rates between the 2 groups. If argatroban increased the rate of recanalization, one would expect it would also prevent reocclusion. It is possible that failure to detect even a trend in this direction may be owing to the small number of patients experiencing reocclusion. Another explanation could be the prolonged time to achieve target levels of anticoagulation in 5 (36%) of the 14 patients. Future studies should evaluate a dosing algorithm that would result in a more consistent time to target aPTT.

Additional limitations include possible selection bias, nonblinded investigators, historical controls, and a lack of long-term outcome data. However, these design characteristics are typical of small preliminary safety analyses and are offset by the potential patient benefits of new appropriately controlled and monitored therapies.

In conclusion, low-dose argatroban combined with IV rtPA may be safe and may produce faster and more complete recanalization than does rtPA alone. The historical comparison described herein reveals the potential for clinical benefit, as well as the possibility of increased risk associated with the use of both drugs. The second phase of the study, to enroll 50 more patients in the open-label trial to ensure that PH-2 levels are below 10%, is now under way. The equilibrium point in the assessment of the risk-benefit balance of this combined therapy can ultimately be established only in an adequately powered, blinded clinical trial with appropriate interim monitoring for early benefit and harm.

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REFERENCES


Trial Registration Required. In concert with the International Committee of Medical Journal Editors (ICMJE), Archives of Neurology will require, as a condition of consideration for publication, registration of all trials in a public trials registry (such as http://ClinicalTrials.gov). Trials must be registered at or before the onset of patient enrollment. This policy applies to any clinical trial starting enrollment after July 1, 2003. For trials that began enrollment before this date, registration will be required by September 13, 2005, before considering the trial for publication. The trial registration number should be supplied at the time of submission.

For details about this new policy, and for information on how the ICMJE defines a clinical trial, see the editorial by DeAngelis et al in the January issue of Archives of Dermatology (2005;141:76-77). Also see the Instructions to Authors on our Web site: www.archneurol.com.