Abciximab in Acute Ischemic Stroke
A Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study

The Abciximab in Ischemic Stroke Investigators

Background and Purpose—Abciximab is a potent parenterally administered platelet glycoprotein IIb/IIIa antagonist. Because this agent has been shown to improve outcomes in coronary artery disease, there is interest to evaluate whether it could improve cerebral perfusion and outcomes after ischemic stroke. This study was designed to evaluate the safety of abciximab in acute ischemic stroke and to obtain pilot efficacy data.

Methods—We conducted a randomized, double-blind, placebo-controlled, dose-escalation trial. Seventy-four eligible and consenting patients presenting within 24 hours after ischemic stroke onset at 38 study sites were randomly allocated to receive either an escalating dose of abciximab (54 patients) or placebo (20 patients) in a ratio of 3:1. We studied 4 escalating doses of abciximab. Patients underwent a scheduled follow-up head CT scan 24 to 36 hours after the completion of study agent administration to monitor for bleeding complications and were evaluated through 3 months.

Results—There were no cases of major intracranial hemorrhage. Asymptomatic parenchymal hemorrhages were detected on post–study agent CT in 4 of 54 abciximab patients (7%) and in 1 of 20 placebo patients (5%). Six additional abciximab patients had asymptomatic hemorrhagic lesions detected by unscheduled brain imaging during their follow-up period. Nine of 11 patients with asymptomatic hemorrhage had a baseline National Institutes of Health Stroke Scale score >14. At 3 months, there was a trend toward a higher rate of minimal residual disability (Barthel Index ≥95 or modified Rankin scale ≤1) among abciximab patients compared with those who received placebo.

Conclusions—Abciximab appears to be safe when administered up to 24 hours after stroke onset, and it might improve functional outcome. (Stroke. 2000;31:601-609.)

Key Words: platelet aggregation inhibitors ■ randomized controlled trials ■ stroke, ischemic
coronary vessels. Also, in the setting of myocardial infarction, the combination of abciximab, aspirin, and adjusted-dose heparin, supplemented by a reduced dose of rtPA or reteplase, yielded coronary patency rates adjusted-dose heparin, supplemented by a reduced dose of infarction, the combination of abciximab, aspirin, and GP IIb/IIIa antagonists may improve flow in both the coronary and cerebral microcirculations.

In view of the success of abciximab in the treatment of acute coronary artery lesions, interest has grown in the use of this agent in acute ischemic stroke. There are also anecdotal reports of the successful use of this agent in cerebrovascular interventional procedures. However, the safety of abciximab in acute ischemic stroke has not been established. In the percutaneous coronary intervention trials, intracranial hemorrhage (ICH) occurred infrequently, with average rates of 0.15% and 0.10% among abciximab and placebo patients, respectively. We therefore performed a randomized, double-blind, placebo-controlled, dose-escalation study of abciximab in patients with acute ischemic stroke. This study examined safety in a broad range of stroke patients, including those presenting up to 24 hours from onset. Although efficacy trials with this agent will most likely focus on a narrower time interval from stroke onset, ie, 6 hours, obtaining safety data in a broader interval provides additional reassurance and would be important for possible extension of the therapeutic window beyond 6 hours in the future.

Subjects and Methods

Study Objectives

The primary objective of the study was to evaluate the risk of fatal and nonfatal major ICH within 5 days after treatment. The main secondary objectives were to assess (1) the rate of asymptomatic parenchymal hemorrhage detected by CT 24 to 36 hours after the end of treatment with study agent; (2) the rate of all ICHs through 3 months; (3) the rates of stroke progression, systemic hemorrhage, and thrombocytopenia within 5 days of treatment; (4) the rates of neurological improvement at 5 days and 3 months; (5) the rates of recurrent strokes within 3 months; and (6) disability outcomes at 3 months.

Patients

The study population consisted of adult ischemic stroke patients evaluated within 24 hours from stroke onset at 38 participating sites (26 in the United States and 12 in Europe). The interval from stroke onset was defined as the time elapsed between the first symptoms of stroke and randomization. For patients whose stroke started during their sleep, the time of onset was defined as the time when the patient was last known to be intact. All patients had a head CT before randomization and had to have a minimum National Institutes of Health Stroke Scale (NIHSS) score of 4. Other reasons for exclusion and the number of patients excluded in each category are listed in the Results section. Patients could have >1 reason for exclusion. Written informed consent was obtained for all study participants.

Randomization and Dosing Regimens

Four dose tiers of abciximab were evaluated against placebo in a dose-escalating sequence (Figure 1). A separate randomization was performed within each of the 4 strata defined by time from stroke onset (<12 hours or 12 to 24 hours) and stroke severity (prerandomization NIHSS score 4 to 14 or >14). If a randomized patient was not treated, an additional patient was randomized to balance the treatment experience of the trial. Before dose escalation occurred, patients in all strata had to be enrolled at a given dose tier. There was no stratification by study site.

Treatment allocation was obtained by contacting a 24-h/d interactive voice-response system located at the Randomization Center. Based on the prespecified stratification criteria, each patient was assigned a study agent kit containing either abciximab or an identical-appearing placebo. The study agent was administered as an intravenous bolus given over ~1 minute during the first 2 dose tiers of the study, whereas the bolus was followed by a 12-hour continuous intravenous infusion for the last 2 dose tiers (Figure 1). The day of randomization was defined as day 0.

Assessments

Neurological status was assessed by the NIHSS at baseline (ie, prerandomization), daily until day 5 or hospital discharge if sooner, and at 3 months (±14 days). The trial mandated a non–contrast-enhanced head CT scan 24 to 36 hours after the end of study agent administration. Additional brain imaging studies were performed at the discretion of the treating physician, including for cases of new or worsening neurological symptoms. Data on the reasons for the additional scans were not collected. Patients underwent telephone-based interviews at ~10 days and 6 weeks after randomization and had a clinic visit at 3 months. Disability outcomes were rated according to the modified Rankin scale and Barthel Index scores at 3 months. Laboratory surveillance included platelet counts daily through day 3 and hemoglobin and hematocrit measurements on day 1 and day 5.

End-Point Definitions

Fatal ICH was defined as autopsy- or imaging-confirmed hemorrhage ascribed to the primary cause of death. Nonfatal major ICH was defined as either symptomatic parenchymal hemorrhage or CT evidence of intraventricular, subdural, or subarachnoid hemorrhage, with or without clinical symptoms. Symptomatic parenchymal hemorrhage was defined as CT-documented bleeding either in the area of the qualifying stroke and causally related to neurological deterioration (≥4 points worsening on the NIHSS compared with the previous examination or by global clinical assessment) or in a different vascular territory and associated with new neurological deficit. Asymptomatic hemorrhagic transformation was defined as CT-documented bleeding in the area of the qualifying stroke without neurological deterioration ascribed to the bleeding. Nonintracranial hemorrhage was assessed by the TIMI criteria. Thrombocytopenia
Between February and November 1998, 3440 patients were enrolled in the study. A regression model testing. Subgroup analyses of safety or efficacy based on either of the stratification variables (severity of stroke or interval from stroke) were not performed because of the small numbers of patients enrolled in the groups. A regression model was classified as moderate (<100 000/mm³ and a 25% decrease from baseline value) or severe (<50 000/mm³). Stroke progression was defined as neurological deterioration in the absence of ICH. Recurrent stroke was defined as recurrence of neurological deficit within the infarct territory after day 5 or deficit in a newly involved territory at any time during the study without ICH or other causes for the neurological symptoms. Neurological improvement was assessed at day 5 and 3 months and defined as either a ≥4-point improvement on the NIHSS compared with the prerandomization score, an NIHSS score of 0, or global clinical impression.

**Ancillary Care**

Patients were admitted to a monitored bed or skilled care unit for the first 24 hours after randomization. They received customary local care for treatment of their stroke, including rehabilitation and management of comorbid diseases. Antiplatelet agents, NSAIDS, or anticoagulants could not be administered until after the results of the 24- to 36-hour post–study agent CT were available. Subsequent therapy for secondary prevention was at the discretion of the local physician.

**Safety Monitoring**

An External Safety Monitoring Board (ESMB) composed of clinicians and scientists not otherwise involved in the study reviewed safety data before escalation to the next dose tier and after each potential major ICH. Mandatory enrollment pauses were instituted before dose escalation and after each potential major ICH, pending ESMB review. These safety reviews were conducted without knowledge of treatment assignment, but the ESMB had the prerogative to become unblinded, if necessary. Upon ESMB recommendation, the Steering Committee would either approve dose escalation, continue enrollment in an ongoing dose tier, or halt/stop enrollment. The chairperson of the Steering Committee, unaware of treatment allocation, reviewed all expedited reports of serious adverse experiences in an ongoing fashion.

**Avoidance of Bias**

All CT scans were reviewed by an independent neuroradiologist blinded to treatment allocation, time period of the examination, and clinical data. MRI studies performed outside the protocol to investigate possible outcome events were also reviewed in a blinded fashion by the same neuroradiologist. An independent reviewer adjudicated all cases of death, ICH, stroke progression, and recurrent stroke without knowledge of treatment allocation. Another independent reviewer adjudicated cases of thrombocytopenia without knowledge of treatment allocation. Results of these adjudicated reviews only were used for final data analyses.

**Statistical Analysis**

Data from all sites were pooled by treatment within each dose tier. Data from placebo patients in all dose tiers were pooled together. Analyses were performed on the intent-to-treat population consisting of all randomized patients, irrespective of whether they received any study agent. Fisher’s exact test was used for all statistical hypothesis testing. Subgroup analyses of safety or efficacy based on either of the stratification variables were not performed in view of the small sample size of the study. Patients who died were assigned the worst score on all measurement scales. Subgroup analyses for either safety or efficacy based on either of the stratification variables (severity of stroke or interval from stroke) were not performed because of the small numbers of patients enrolled in the groups. A regression model with length of stay as the dependent variable and age, sex, baseline NIHSS score, time from stroke onset to randomization, and treatment received as the independent variables was used to examine the effect of abciximab on length of hospital stay.

**Results**

Between February and November 1998, 3440 patients were evaluated for possible enrollment in the study (Figure 1). A total of 3177 patients were excluded for ≥1 of the following reasons: NIHSS <4 (1293 patients); American patients ≤3 hours from stroke onset or any patient with stroke onset >24 hours earlier (749 patients); hemostatic defect or increased hemorrhagic risk (418 patients); severe illness or disability (383 patients); stratum complete for given dose tier or enrollment pause for ESMB evaluation (364 patients); need for antiplatelet agent, NSAID, or anticoagulant (89 patients); stupor or coma (88 patients); participation in another trial (64 patients); suspected subarachnoid hemorrhage (44 patients); hypertension (37 patients); hypodensity involving the entire MCA territory (21 patients) or mass effect (14 patients) on baseline CT; cerebral venous thrombosis (14 patients); vasculitis (11 patients); suspected septic embolism (5 patients); pregnancy or lactation (3 patients); unavailability of study agent at site (10 patients); alcohol abuse or illicit drugs (2 patients); and previous administration of abciximab (1 patient). Informed consent was obtained from 74 of the remaining 263 eligible patients, 54 of whom were allocated to receive abciximab and 20 to the placebo group.

Twenty-seven of 38 participating sites (71%) enrolled the 74 study patients; 18 of these sites were in the United States and 9 in Europe. Forty-nine patients were enrolled in the United States and 25 in Europe. The baseline characteristics of the study patients, including demographic variables, risk factors, and stroke features, are described in Table 1. The average age of the total study population, consisting of all abciximab and placebo patients, was 66±15 years. There was no racial imbalance or difference in mean body weight and blood pressure among the patient groups. The majority of patients had cortical lesions involving the MCA territory, and ~50% had signs of early infarction on baseline CT. A higher proportion of placebo than abciximab patients had cortical lesions. Thirty-six of 74 patients (49%) had left-sided brain lesions, 37 (50%) had right-sided lesions, and 1 (1%) had bilateral lesions.

The median time since stroke onset for all 74 patients was 12 hours (range, 2 to 23 hours), and the median baseline NIHSS score was 15 (range, 4 to 25). The mean and median times from stroke onset to start of study agent for all 70 patients who received study agent were 13±6 hours and 12 hours, respectively (range, 2 to 24 hours). Seven of 74 patients (9%) had a baseline NIHSS score >20. The median time after stroke onset was longer in the 0.15-mg/kg bolus group than in the other abciximab dose groups and placebo patients. Two patients were treated within 3 hours of stroke onset: 1 abciximab patient in the 0.25-mg/kg bolus plus infusion group and 1 placebo patient. Four patients, 2 in the abciximab 0.15-mg/kg bolus group and 2 in the placebo group, did not receive study agent. In 1 abciximab and 2 placebo patients, the blood pressure became unacceptably high after randomization and could not be stabilized to initiate treatment within the planned time window. The fourth patient, in the abciximab group, inadvertently received a single 5-mg dose of warfarin in the interval between randomization and starting study agent. No patients were lost to follow-up.
Twelve patients (16%) died during the course of the study: 2 within the first 5 days and 10 between day 6 and 3 months (Table 2). Nine of 54 abciximab patients (17%) and 3 of 20 placebo patients (15%) died. The causes of death among abciximab patients were as follows: direct consequence of the qualifying stroke (3 patients at days 1, 5, and 7); sudden cardiac death (1 patient at day 14); pneumonia (3 patients at days 13, 30, and 70); and withdrawal of life support after major sequelae from a very severe initial stroke (2 patients at days 47 and 64). The 3 deaths within the first week of enrollment were the result of brain edema among patients with very severe strokes. The causes of death among placebo patients were sudden cardiac death (2 patients at days 11 and 49) and pneumonia (1 patient at day 37). None of the deaths were judged to be due to the study agent or ICH.

There were no identified cases of fatal or nonfatal major ICH within either 5 days or 3 months of randomization. In a single instance, a local investigator judged 1 patient as having symptomatic parenchymal hemorrhage, but the patient’s scores on the NIHSS did not worsen. The blinded reviewer subsequently adjudicated this event as an asymptomatic hemorrhagic transformation of the infarction.

### Safety Outcomes

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### Asymptomatic Parenchymal Hemorrhages

Asymptomatic parenchymal hemorrhages were detected on the post–study agent head CT in 4 of 54 abciximab patients (7%) and in 1 of 20 placebo patients (5%). One of the asymptomatic hemorrhages among abciximab patients oc-
curred in the 0.20-mg/kg bolus dose group and 3 in the 0.25-mg/kg bolus plus infusion dose group.

Thirty-one of 54 abciximab patients (57%) and 9 of 20 placebo patients (45%) underwent additional brain imaging studies (ie, CT or MRI) during the course of the study. Asymptomatic hemorrhagic lesions were detected in 6 abciximab patients on these additional imaging studies: 1 at day 2 (0.25 mg/kg bolus plus infusion), 1 at day 3 (0.20 mg/kg bolus), 1 at day 5 (0.20 mg/kg bolus), 2 at day 6 (0.15 mg/kg bolus and 0.25 mg/kg bolus plus infusion), and 1 at day 35 (0.20 mg/kg bolus). Five of these 6 patients did not have parenchymal hemorrhage on their post–study agent CT, and this examination was not performed in the 0.25-mg/kg bolus plus infusion patient whose hemorrhage was detected at day 6. Thus, asymptomatic parenchymal hemorrhage was detected in 10 of 54 abciximab patients (19%) and in 1 of 20 placebo patients (5%) through 3 months (*P value for dose-relationship, 0.07). Five of the asymptomatic hemorrhages occurred at the 0.25-mg/kg bolus plus infusion abciximab dose (Table 2).

The clinical characteristics and CT scan features of patients with asymptomatic parenchymal hemorrhage are shown in Table 2.

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<th>Abciximab 0.15 B</th>
<th>Abciximab 0.20 B</th>
<th>Abciximab 0.20 B +1</th>
<th>Abciximab 0.25 B +1</th>
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<td>1</td>
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<td>Total</td>
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<tr>
<td>Total</td>
<td>4 (20%)</td>
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<td>3</td>
<td>2</td>
<td>3</td>
<td>10 (19%)*</td>
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<td></td>
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<td>7</td>
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<td>10</td>
<td>10</td>
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<td>4</td>
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<td>5</td>
<td>6</td>
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<td>7</td>
<td>7</td>
<td>6</td>
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<td>11</td>
<td>5</td>
<td>7</td>
<td>7</td>
<td>30 (56%)</td>
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<td>≥95</td>
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<td>6</td>
<td>7</td>
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<td>&lt;60</td>
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<td>3</td>
<td>5</td>
<td>5</td>
<td>20 (37%)</td>
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</table>

Neurological improvement indicates a gain of ≥4 points. Abbreviations as in Table 1. *P value for dose-relationship = 0.07.
patients (50%) and 8 of 20 placebo patients (40%) had Barthel index scores ≥95 at 3 months.

Length of Hospital Stay
A regression model adjusting for age, sex, baseline NIHSS, and time from stroke onset showed a nonsignificant reduction in mean length of hospital stay of 4 days in favor of abciximab (P=0.39). The mean lengths of stay in abciximab and placebo patients were 13±16 days and 17±19 days, respectively. The median lengths of stay in abciximab and placebo patients were 7 and 12 days, respectively.

Discussion
This is the first in a series of planned studies to evaluate the potential usefulness of abciximab in the treatment of acute ischemic stroke. The primary objective of the study was to obtain preliminary safety data on abciximab in a broad spectrum of patients with acute ischemic stroke. Additional objectives were to select a dosing regimen for abciximab that could be evaluated in future studies and to obtain preliminary efficacy data. The stroke severity of patients in this trial compares favorably to that obtained in the National Institute of Neurological Disorders and Stroke rtPA trial, at least from the aspect of baseline NIHSS score.

Symptomatic parenchymal hemorrhage is the most feared complication of reperfusion treatment for acute ischemic stroke. Abciximab, combined with aspirin and adjusted-dose heparin, is associated with a low risk of ICH in the setting of percutaneous coronary intervention. Before this study, there were no data on the risk of ICH after abciximab therapy for acute ischemic stroke. In this study, abciximab was used alone, without concomitant aspirin or heparin. Our results suggest that abciximab at doses used in treatment of coronary artery disease is relatively safe in acute ischemic stroke, even when a 24-hour treatment window is used.

There was a higher frequency of asymptomatic parenchymal hemorrhage in abciximab patients than in placebo pa-
Moderate thrombocytopenia occurred in 7% of abciximab patients. Thrombocytopenia is a well-recognized complication of abciximab and other GP IIb/IIIa antagonists.\textsuperscript{10–14} There were no adverse consequences related to this complication in this study. The differential diagnosis of thrombocytopenia in abciximab-treated patients includes true thrombocytopenia and platelet clumping.\textsuperscript{32} Although the numbers are small, the frequency of thrombocytopenia obtained in this trial was higher than that reported in the percutaneous coronary intervention trials.\textsuperscript{11–14} Whether this was a chance occurrence or because abciximab was given without concomitant aspirin or heparin is unknown and will require further evaluation.

A secondary objective of the study was to select a dose of abciximab for future studies. Data from the percutaneous coronary intervention studies provide insight on the most
effective regimen of abciximab and the intensity of GP IIb/IIIa receptor blockade required to achieve efficacy. The 0.25-mg/kg bolus plus 12-hour infusion regimen has shown the best clinical efficacy in percutaneous coronary intervention, whereas a 0.25-mg/kg bolus-only dose yielded suboptimal results. The benefit of the 12-hour infusion may be related to passivation (ie, nonreactive state) of the vessel wall at the site of injury. We elected not to study a dose higher than the approved percutaneous coronary intervention regimen, a decision partly influenced by the observation that the dose of rtPA in stroke is lower than that in myocardial infarction. Also in myocardial infarction, a higher dose of abciximab has been associated with a higher bleeding rate.

On the basis of these considerations, we would select the 0.25-mg/kg bolus plus 12-hour infusion regimen to be brought forward in future trials. After stroke, the infusion regimen could prevent delayed platelet aggregation in the microcirculation and reduce inflammation by binding to the Mac-1 integrin, thus halting progression of thrombosis or recurrent edema.

Analysis of the pooled abciximab data provides some preliminary evidence that this agent might improve outcome after stroke. The proportion of patients with minimal residual disability at 90 days was higher in the abciximab group.

In summary, the results of this study suggest that abciximab deserves further evaluation in the setting of acute ischemic stroke. The absence of major ICH is encouraging. These initial results will help us in designing the most appropriate follow-up study.

Appendix

Study Organization

Steering Committee
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