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Gavestinel Does Not Improve Outcome After Acute Intracerebral Hemorrhage

An Analysis From the GAIN International and GAIN Americas Studies

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Background and Purpose—Glycine Antagonist in Neuroprotection (GAIN) International and GAIN Americas trials were prospectively designed, randomized, placebo-controlled trials of gavestinel, a glycine-site antagonist and putative neuroprotectant drug administered within 6 hours of suspected ischemic or hemorrhagic stroke. Both trials reported that gavestinel was ineffective in ischemic stroke. This analysis reports the results in those with primary intracerebral hemorrhage.

Methods—The primary hypothesis was that gavestinel treatment did not alter outcome, measured at 3 months by the Barthel Index (BI), from acute intracerebral hemorrhage, based on pooled results from both trials. The BI scores were divided into 3 groups: 95 to 100 (independent), 60 to 90 (assisted independence), and 0 to 55 (dependent) or dead.

Results—In total, 3450 patients were randomized in GAIN International (N=1804) and GAIN Americas (N=1646). Of these, 571 were ultimately identified to have spontaneous intracerebral hematoma on baseline head computerized tomography scan. The difference in distribution of trichotomized BI scores at 3 months between gavestinel and placebo was not statistically significant ($P=0.09$). Serious adverse events were reported at similar rates in the 2 treatment groups.

Conclusions—These observations from the combined GAIN International and GAIN Americas trials suggest that gavestinel is not of substantial benefit or harm to patients with primary intracerebral hemorrhage. These findings are similar to results previously reported in patients with ischemic stroke. **(*Stroke*. 2005;36:1006-1010.)**

Key Words: hemorrhage ■ neuroprotection ■ stroke

One of the major potential advantages of a successful neuroprotectant drug for acute stroke would be its relative safety compared with thrombolytic therapy. In fact, the ideal neuroprotectant drug should be safe enough that it could be administered to patients with suspected acute stroke, either ischemic or hemorrhagic, before neuroimaging, thereby expediting treatment during the critical time window when the biochemical events leading to infarction are in progress and potentially modifiable. Moreover, some investigators have suggested that treatment with neuroprotective drugs early in the course of primary intracerebral hemorrhage might lessen the damage related to the hemorrhage and improve outcome.[1,2]

Such a strategy was used in the design of 2 large multicenter randomized, placebo-controlled clinical trials of gavestinel, a specific antagonist at the glycine site of the N-methyl-D-aspartate receptor, for acute stroke. The details of the design and results of each of these trials, GAIN International[3] and GAIN Americas,[4] have been published previously. In both trials, patients with intracerebral hemorrhage were eligible for inclusion, although the primary analysis was performed only on those patients who did not have hemorrhagic stroke on a baseline head computerized tomography scan obtained either before or within 12 hours of the initial dose of study medication. Preliminary experience in human trials with gavestinel treatment of intracranial hemorrhage was sparse.[5,6] This report focuses on the safety and potential efficacy of gavestinel in a much larger pooled population of patients in GAIN International and GAIN Americas who had hemorrhagic stroke.

Patients and Methods

This study was prospectively designed to test the safety and preliminary efficacy of gavestinel in acute primary intracerebral hemorrhage. The primary null hypothesis to be tested was that gavestinel treatment did not alter outcome from acute intracranial hemorrhage when begun within 6 hours of the onset of symptoms. This hypothesis was a secondary hypothesis of each of the main trials. Another secondary hypothesis was that serious adverse events were not more frequent with gavestinel treatment than with placebo. It was recognized that neither Glycine Antagonist in Neuroprotection

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*The GAIN Americas and GAIN International Investigators are listed in the Appendices to References 3 and 4.

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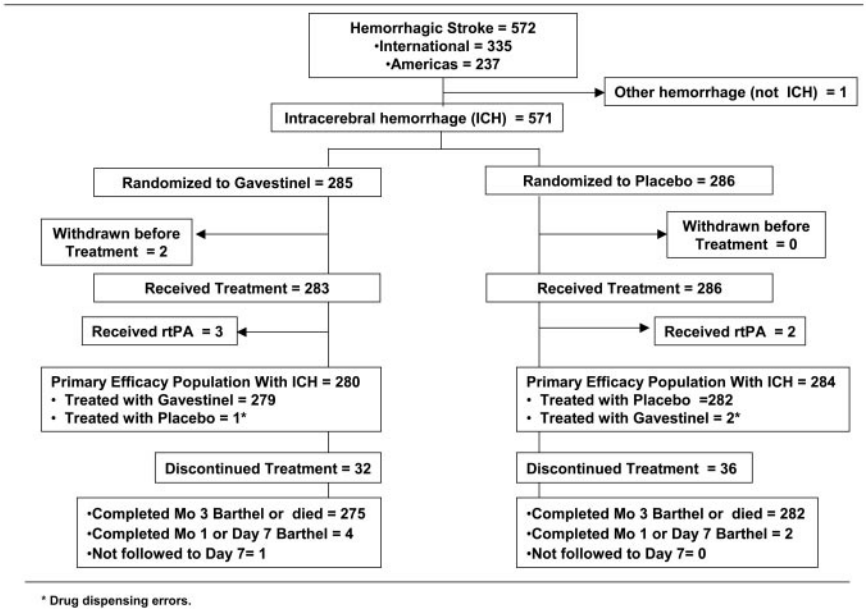

Figure 1. Trial profile.

(GAIN) International nor GAIN Americas would enroll sufficient numbers of patients with intracranial hemorrhage to make any important inferences regarding either safety or efficacy of gavestinel, so an analysis pooling the results from both trials was planned prospectively. Because the target sample sizes were determined by the number of nonhemorrhagic patients, there was no prespecified effect size, power calculation, or sample size with respect to the intracerebral hemorrhage patients. The protocols and consent forms used for both trials were reviewed and approved by each participating institution's institutional review board before beginning enrollment.

The inclusion and exclusion criteria for both GAIN International and GAIN Americas were nearly identical and have been published previously.[3,4] In summary, patients had to have had a suspected acute ischemic or hemorrhagic stroke and have treatment begun within 6 hours of the onset of symptoms. Eligible patients should not have had pre-existing disability and had to be awake or only slightly drowsy with at least a mild motor deficit at the time treatment was begun. Baseline head computerized tomography scans using a standard protocol with at least 10-mm slice thickness were required either before treatment or within 12 hours of the first dose. The scans from both trials were sent for review by a central adjudication committee comprising 3 independent neuroradiologists (see Appendix 1) who classified each scan as either showing intracranial hemorrhage or not. Those scans showing hemorrhage were subclassified into categories as follows: primary intracerebral hematoma, hemorrhagic infarction, subarachnoid hemorrhage, subdural hemorrhage, and intraventricular hemorrhage using standard published criteria.[7,8] Those patients judged to have primary intracerebral hematoma are the subject of this report.

After informed consent was obtained, patients were randomly assigned (1:1) to receive either gavestinel or placebo, with stratification by age (75 or younger or older than 75 years) and stroke severity (National Institutes of Health Stroke Scale [NIHSS][9] scores categorized as 2 to 5, 6 to 13, ≥14) yielding 6 strata. The study drug was given intravenously over 3 days. Patients received either placebo or a total of 1800 mg of gavestinel administered as a loading dose of 800 mg over 4 hours, followed by 5 maintenance doses of 200 mg each over 15 minutes at 12, 24, 36, 48, and 60 hours after the start of the loading dose. Study treatment was terminated if creatinine values exceeded 2.0 mg/dL (178.8 μmol/L) or if bilirubin, aspartate aminotransferase, or alanine aminotransferase values exceeded 4-times the upper limit of reference ranges.

The primary outcome was functional capability in activities of daily living at 3 months as measured by the Barthel Index (BI).[10] BI scores were trichotomized as follows: 95 to 100 indicates independence (little or no help required), 60 to 90 indicates assisted independence (some help required), and 0 to 55 indicates dependence (help required with most or all activities). Deaths were included with the 0 to 55 group for the primary analysis but analyzed separately for safety. The BI cut points were chosen based on previous studies that established that scores of 60 and 95 defined meaningful clinical subgroups.[11,12] To minimize bias, the person performing the BI at 3 months could not be a person involved in caring for the patient during the initial hospitalization.

Secondary outcome measures included the BI at 7 days or hospital discharge (whichever came sooner) and at 1 month; NIHSS score at 1 and 3 months; and the modified Rankin Scale[13] at 1 and 3 months. Additionally, a global outcome statistic similar to that used in the National Institute of Neurological Disorders and Stroke rtPA Stroke Trial[12] was calculated.

Adverse events, both serious (eg, life-threatening, resulting in death, or prolonging hospitalization) and nonserious, were recorded in a contemporaneous fashion. Routine blood work obtained at baseline and at the end of treatment was sent to a central laboratory to screen for hematological, renal, and hepatic dysfunction. The safety of participants in the trial was overseen by an independent Safety and Efficacy Data Monitoring Committee (see Appendix 1).

Statistical Analysis

In each GAIN trial, the test of the primary null hypothesis used the extended Mantel–Haenszel χ^2 test (1 degree of freedom), stratified by baseline stroke severity and age group, to combine the evidence from the 6 strata. This took account of the stratified randomization, which minimizes any confounding arising from age and NIHSS differences between strata. In the current analysis, the same approach was prespecified for the test of the primary null hypothesis. The data from the 12 strata (6 from each trial) were combined in a similarly stratified analysis using the extended Mantel–Haenszel procedure; $P<0.05$ (2-sided) was considered statistically significant.

This procedure assumes that the odds ratios for treatment in the 2 trials are the same (the intracerebral hemorrhage rates in each may differ). A likelihood ratio test was used to test this assumption. A significant difference (ie, $P<0.05$) would indicate a treatment by trial interaction and that an analysis that combined the data from the 2 trials would be inappropriate. A stratified Cox proportional hazards model compared survival over 3 months in the 2 trials. Both results indicated that the data could be combined ($P=0.18$, for the primary analysis and $P=0.29$, for survival).

TABLE 1. Baseline Characteristics of Patients With Intracerebral Hematoma in GAIN Americas and GAIN International*

	Gavestinel	Placebo
No.	280	284
Age, mean±SD	67.5±12.0	68.5±12.2
Proportion male, No. (%)	165 (58.9)	173 (60.9)
Proportion white, No. (%)	222 (79.3)	229 (80.6)
Baseline blood pressure:		
Systolic, mm Hg (mean±SD)	172.0±27.4	169.9±26.8
Diastolic, mm Hg (mean±SD)	92.8±16.4	92.3±16.5
Baseline NIHSS score, median (interquartile range)	15.0 (9.0–18.0)	13.0 (9.0–18.0)
Time from onset to treatment, min (median, interquartile range)	278.0 (235.0–330.0)	290.0 (240.0–330.0)
Hemorrhage characteristics		
Small, ≤2.5 cm, No. (%)	66 (23.6)	58 (20.6)
Large, >2.5 cm, No. (%)	214 (76.4)	224 (79.4)
Intraventricular extension, No. (%)	79 (28.2)	75 (26.4)

*None of the differences between gavestinel and placebo groups is statistically significant at $P \leq 0.05$ 2-sided. All comparisons take stratification into account. A 2-way analysis of variance for treatment group by stratum was used for age and baseline blood pressure, a stratified Wilcoxon test for baseline NIHSS score and time from onset to treatment, and a Mantel–Haenszel test across strata for proportion male, proportion white, and hemorrhage characteristics.

All comparisons of baseline characteristics in gavestinel versus placebo groups take stratification into account. A 2-way analysis of variance for treatment group by stratum was used for continuous variables, a stratified Wilcoxon rank-sum test for ordinal measures, and a Mantel–Haenszel test across strata for categorical variables.

Results

From March 1998, through October 1999, 3450 patients were randomized in GAIN International (N=1804) and GAIN Americas (N=1646). Of these, 572 were judged by the Image Adjudication Committee to have hemorrhagic stroke on the baseline head computerized tomography scan (Figure 1). One was not located intracerebrally, leaving 571 actual intracerebral hemorrhages. Two patients did not receive treatment and were excluded from the analysis. Additionally, 5 patients (3 gavestinel and 2 placebo) were excluded because they had received tissue plasminogen activator before randomization. One patient randomized to gavestinel instead received placebo, whereas 2 patients randomized to placebo received gavestinel. For the primary efficacy analysis, which used intent-to-treat principles, there were 280 patients assigned gavestinel versus 284 patients assigned placebo. The safety analyses included all randomized and treated patients according to the drug they actually received: 284 gavestinel patients versus 285 placebo patients. Seven patients were missing 3-month BI scores. Earlier post-treatment assessments were carried forward for 6 of these (4 gavestinel and 2 placebo). One gavestinel patient was completely lost to follow-up and was imputed to have the lowest possible BI score.

Table 1 outlines the baseline characteristics of the patients in each treatment group. There was an approximate balance in the age, race, sex, and time from onset of symptoms to initiation of treatment. There were similar proportions of patients who had small versus large hematomas and intraventricular extension of the hemorrhage. Despite the stratified randomization, the gavestinel group had a median 2 point higher baseline NIHSS score than placebo patients did. None of the differences in baseline characteristics was statistically significant.

Mortality was not significantly different between the 2 groups (stratified Wald test z score=−0.878, P=0.380; relative hazard ratio=0.843, 95% confidence interval=0.575 to 1.235). In the efficacy population, 51 of 280 (18%) gavestinel-treated patients died within 3 months compared with 58 of 284 (20%) placebo patients. In the safety population (n=569), 54 of 284 (19%) gavestinel patients died compared with 59 of 285 (21%) placebo patients.

Figure 2 shows the distribution of BI scores at 3 months in the 2 treatment groups divided into the prespecified cutoffs for independence, assisted independence, and dependence or death. Overall, the difference in distribution of 3-month BI scores favored gavestinel but did not reach statistical significance (P=0.091). Inclusion of the 5 patients receiving tissue plasminogen activator did not significantly alter the results (P=0.128). Analyses of the secondary outcomes, including the modified Rankin Scale and NIH Stroke Scale, failed to disclose any statistically significant differences (Appendix 2).

The proportion of patients who reported serious adverse events was similar in both groups (Table 2). There were no important differences between the groups in the incidence of nonserious adverse events, except that the proportion of patients with elevated bilirubin (a known side effect of gavestinel) was 14% in the gavestinel group compared with 5% in the placebo group. All bilirubin elevations were transient.

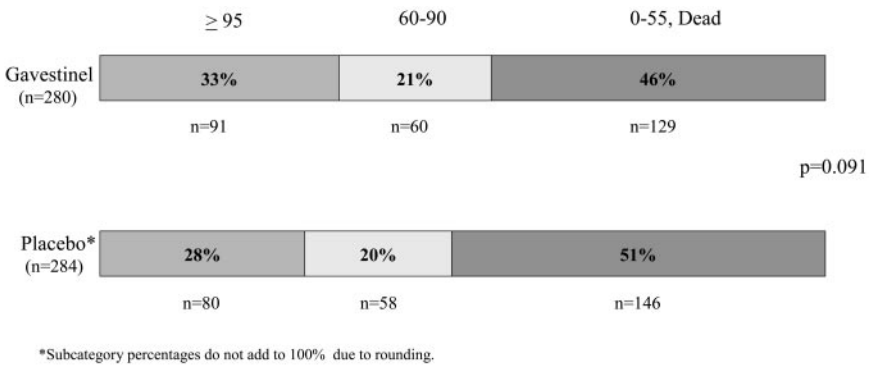

Figure 2. Distributions of BI scores and mortality at 3 months. Differences in outcome were not statistically significant (extended Mantel–Haenszel χ^2 test).

TABLE 2. Selected Serious Adverse Events in Intracerebral Hematoma Patients in GAIN Americas and GAIN International

	Gavestinel n=284 (%)	Placebo n=285 (%)
Progression of stroke	82 (29)	88 (31)
Herniation	23 (8)	26 (9)
Serious respiratory*	5 (2)	9 (3)
Any SAE	51 (18)	63 (22)

*Pneumonia, aspiration, pulmonary edema, etc.
SAE indicates serious adverse event.

Discussion

This pooled analysis represents the largest clinical trial of a putative neuroprotectant drug in patients with primary intracerebral hemorrhage. This group of stroke patients has long been neglected in stroke research. Previous studies have largely focused on surgical interventions.[14,15] Unfortunately, no statistically significant benefit of gavestinel treatment begun within 6 hours of intracerebral hemorrhage was seen in this trial. These results are consistent with the reported observations in ischemic stroke patients treated with gavestinel.[3,4]

The patients enrolled in this study were a highly selected subgroup of patients with intracerebral hemorrhage. To be eligible, patients had to be fully alert or only slightly drowsy, and had to have at least a mild motor deficit. That ≈20% of patients died within 3 months suggests that if patients with intracerebral hemorrhage are selected with similar neurological criteria at baseline, their outcomes may not be worse than patients with similar deficits from ischemic stroke.[3,4] Similarly, the overall rate of serious adverse events (≈20%) reported in this hemorrhagic stroke population was similar to the rate reported in the ischemic stroke population.

Although this was a large clinical trial in intracerebral hemorrhage by historical standards, it is possible that a beneficial treatment effect of gavestinel may have been missed because of a type 2 error. The observed adjacent odds ratio and 95% confidence interval was 1.22 (0.98 to 1.52) with the current sample size. If the placebo outcomes remained the same and assuming proportional adjacent odds, the proportion of favorable outcomes in the gavestinel group would have had to be an absolute 14% greater (ie, 42% versus 28% for BI ≥95) to have been detectable with 90% power in a study of this size. For good power to detect smaller differences, a much larger sample size would have been required. However, the relatively small absolute 5% difference in favor of gavestinel observed in the current study, combined with the indifferent results obtained from the 2 larger studies in patients with acute ischemic stroke, offer little encouragement for further clinical trials of this compound in patients with intracerebral hemorrhage.

Appendix 1

Image Adjudication Committee: Rudiger von Kummer, MD (Chair), University of Technology, Dresden, Germany; Stefano Bastianello, MD, PhD, State University of Rome, Rome, Italy; Thomas Tomsick, MD, FACR, University of Cincinnati, Cincinati, Ohio.

Safety and Efficacy Data Monitoring Committee: Lawrence Brass, MD (Chair), Yale University, New Haven, Conn.; Joseph Broderick, MD, University of Cincinnati Medical Center, Cincinnati, Ohio; Michael Gent, DSc, McMaster University, Hamilton, Ontario, Canada: Michael Harrison, DM, FRCP, University College Hospital and Medical School, London, England; Philippe Lechat, MD, PhD, Hopital Pitié Salpètrière, pris, France; nonvoting member: Robin Roberts, MTech, McMaster University.

GAIN International Steering Committee: Kennedy Lees, MD (chair), Glasgow, UK; Kjell Asplund, MD, Umea, Sweden; Antonio Carolei, MD, Aquila, Italy; Stephen Davis, MD, Melbourne, Australia; Hans-Christoph Diener, MD, Essen, Germany; Markku Kaste, MD, Helsinki, Finland; Jean-Marie Orgogozo, MD, Bordeaux, France; John Whitehead, PhD, Reading, UK.

GAIN Americas Steering Committee: Ralph Sacco, MD, (chair), New York, NY; Stephen Phillips, MD, Halifax, Canada; Clarke Haley, MD, Charlottesville, Va; John Thompson, PhD, New York, NY; Bruce Levin, PhD, New York, NY; nonvoting members: Paul Ordronneau, PhD and Rose Snipes, MD, Glaxo Wellcome, Inc, Research Triangle Park, NC.

APPENDIX 2. Secondary Outcomes at 3 Months

	Gavestinel n=280	Placebo n=284	*P*
Modified Rankin Scale			0.73*
No symptoms	16 (5.7%)	18 (6.3%)	
Symptoms, no disability	41 (14.6%)	33 (11.6%)	
Mild disability	39 (13.9%)	34 (12.0%)	
Moderate disability	39 (13.9%)	39 (13.7%)	
Moderately severe disability	74 (26.4%)	77 (27.1%)	
Severe disability	21 (7.5%)	25 (8.8%)	
Death	50 (17.9%)	58 (20.4%)	
NIHSS			
Median, interquartile range	5 (2–14)	6 (2–17)	0.31†
Global test, (Barthel ≥95, NIHSS 0 or 1, Rankin 0 or 1)			
Odds ratio, (95% confidence interval)	1.067 (0.758–1.402)		0.71‡

*Stratified Generalized Mantel-Haenszel χ^2 test
†Stratified Wilcoxon rank-sum test.
‡Stratified global test.

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