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Effect of the Glycine Antagonist Gavestinel on Cerebral Infarcts in Acute Stroke Patients, a Randomized Placebo-Controlled Trial: The GAIN MRI Substudy

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Abstract

Background and Purpose—Gavestinel, GV150526, is a selective antagonist at the glycine site of the N-methyl-D-aspartate receptor. The safety and efficacy of GV150526 were studied in two phase III randomized placebo-controlled clinical trials of acute ischemic stroke patients within 6 h from onset [The Glycine Antagonist in Neuroprotection (GAIN) International and GAIN Americas Trials]. A planned MRI substudy within these trials investigated the effect of gavestinel on infarct volume.

Methods—Patients enrolled in the GAIN trials at designated MRI substudy sites were eligible if they had a pretreatment acute cortical lesion on diffusion-weighted MRI of at least 1.5 cm diameter or 5 cm³. Final lesion assessment was performed on T₂-weighted MRI at month 3. Blinded image analysis was performed centrally. The primary hypothesis was that gavestinel would attenuate lesion growth from baseline relative to placebo.

Results—A total of 106 patients were eligible, 75 (34 gavestinel, 41 placebo) of whom had month 3 scans (primary analysis population). No effects of gavestinel on infarct volume were observed in the primary or other analyses. However, significant associations of lesion volume to clinical severity and outcomes were observed. Ischemic lesion volume decrease was predictive of substantial clinical improvement.

Conclusion—Consistent with the clinical outcomes in the GAIN trials, no effects of gavestinel on ischemic infarction was observed. Concordance of results of the clinical outcome trials with those of this infarct volume substudy as well the associations of infarct volume to clinical

outcomes further support the potential role of infarct volume as a marker of outcome in dose finding and proof of principle acute stroke trials.

Keywords

Placebo-controlled clinical trial; Gavestinel; Neuroprotection; Diffusion MRI

Many antagonists of the N-methyl-D-aspartate (NMDA) receptor have shown neuroprotective effects in animals, but none has demonstrated benefit in clinical trials of acute stroke patients [1]. The possible reasons that neuroprotective success in animal models has not translated to positive clinical trials and strategies that may improve clinical development have been discussed extensively elsewhere [2–4]. In animal models, a necessary requirement for advancement to clinical trials is a beneficial effect of the drug in reducing infarct volume relative to controls. A common limitation of neuroprotective development has been reliance on only safety (by identification of maximum tolerated dose) as the decisive factor in proceeding from phase II to phase III trials; evidence of target biological drug effects, e.g., infarct volume reduction, at safe doses or any central nervous system effect that would confirm adequate brain penetration has not been a requirement. One approach that has been advocated to improve stroke drug development has been the use of imaging markers of ischemic pathology as tools for selecting patients and measuring drug effects [5].

The hypothesized utilities of MRI with diffusion (DWI) and perfusion (PWI) in ischemic stroke clinical trials are threefold: (1) selection: pretreatment imaging to confirm the diagnosis of acute ischemic stroke and select the optimal target population based on ischemic pathology; (2) proof of principle: outcome measurements in phase II trials aimed at replicating the preclinical effects of the drug on infarct volume or otherwise demonstrating the target pharmacological response, or (3) outcome measures in phase III trials providing confirmatory evidence of a clinical benefit. Although there is no consensus in the choice of clinical outcomes in neuroprotective stroke trials [2, 3, 6], the degree of disability is a more clinically relevant outcome variable than death, although less reliably measured. Outcomes on stroke clinical outcome scales will depend on many factors, including infarct location, patient age and comorbidities, as well as individual investigator judgment. Sample size estimates for stroke neuroprotective trials using clinical outcome scales may range from 500 to 1,350 subjects per group [7–11]. Infarct volume is a direct measure of the final pathological step that mediates the clinical deficits caused by stroke and therefore has been hypothesized to be a more powerful and more reliable measure of relevant drug effects than outcomes measured by clinical disability scales [5, 12]. This hypothesis has been supported by data from natural history series and prior clinical trials.

Preliminary data indicate that the ischemic lesion volume measurements by DWI acutely and T₂-weighted imaging (T2WI) chronically are predictive of the clinical status of patients at acute or chronic times, and of patient outcome [12–15]. Two acute stroke trials of citicoline used MRI to select and evaluate patients by ischemic lesion location and size. The first trial found a trend toward a reduction in lesion volume growth with active therapy (180 to 34%) and estimated that a sample size of 58 per arm would have had sufficient power to

show significance [13]. The second citicoline MRI trial was a substudy of a larger clinical trial and demonstrated significant lesion volume reductions with citicoline treatment in approximately 70 patients per arm [16], an order of magnitude fewer subjects than required to demonstrate benefits on clinical outcome scales [17].

Gavestinel, GV150526, is a selective antagonist at the glycine site of the NMDA receptor, which reduces infarct volume in experimental stroke models [18]. Phase II dose escalation and safety clinical trials [19] confirmed the safety of a dose that was tested in the Glycine Antagonist in Neuroprotection (GAIN) International and GAIN Americas Phase III clinical trials [7, 10], randomized placebo- controlled clinical trials of acute ischemic stroke patients within 6 h from onset. No clinical benefit of gavestinel was observed in the GAIN clinical trials. A prospective MRI substudy was undertaken, however. The primary aim of this substudy was to investigate the treatment effect of gavestinel on ischemic lesion size, as evidenced by a reduction in ischemic lesion volume growth in patients treated with gavestinel relative to those treated with placebo. The secondary objective was to investigate the relationship of lesion volumes to clinical outcomes.

Methods

Study Design

The MRI substudy design paralleled that of the GAIN Americas and GAIN International clinical outcome studies, from which substudy patients were recruited [7, 10] It was a multi-center, randomized, double-blind, placebo-controlled study of a single-dose regimen of gavestinel in the treatment of patients with acute ischemic stroke. Patients in the clinical outcome studies were randomized on a 1:1 basis to receive either gavestinel or placebo by intravenous infusion within 6 h of symptom onset. The full design, eligibility criteria and patient characteristics have been described elsewhere [7, 10].

The substudy was performed in 48 centers in 9 countries. Sites were selected based on demonstrated competence in performing diffusion and perfusion MRI of acute stroke. Patients meeting eligibility and consenting to the clinical outcome studies were screened and scanned for eligibility for the MRI substudy. Randomization into the clinical outcome studies was not dependent on results of the screening baseline MRI or inclusion in the substudy. In an effort to save time within the 6-hour window, sites obtained the baseline MRI at the same time they were making the call for randomization and subsequently reconstituting the study drug. However, the baseline MRI had to be obtained prior to the administration of the study drug. Thus, treatment was initiated upon completion of the scan and did not require interpretation of the scan.

MRI scans were obtained at baseline and at month 3. All were performed on 1.5-tesla standard clinical scanners from 4 manufacturers permitting single shot echo-planar imaging. Pulse sequence parameters were standardized to be equivalent across scanner models.

Acute ischemic lesion was assessed on DWI, using 20 contiguous 7 mm thick slices. The DWI was acquired using b-values at 1,000 and 0 s/mm². PWI was performed as multi-slice gradient echo echo-planar imaging using the bolus tracking method with 0.1 mmol/kg

gadolinium-DTPA injected manually or by power injector at a rate of 5 ml/s. Baseline scans also included T2*-weighted images for hemorrhage detection and MR angiography for depiction of vascular pathology. At month 3 ($\pm$ 3 days) DWI was also obtained.

All MRI data were sent to the MRI Core Laboratory, where image analysis and quantification were performed. All lesion volumes were measured by an expert reader who was blinded to both the patient's treatment assignment and clinical characteristics. Lesion volumes were measured by the planimetric method using commercial software (Cheshire) that permitted semi-automated segmentation followed by user editing of region boundaries. The DWI isotropic $b = 1,000$ images were used to assess the lesion volume at baseline and the DWI $b = 0$ images (equivalent of the T2WI) were used to assess lesion volume at month 3. The abnormal perfusion volume was determined as the region that showed a delay (relative hyperintensity) in the relative mean transit time (MTT) maps calculated from the raw PWI images at the MRI Core Laboratory.

A patient was eligible for inclusion if the acute ischemic lesion involving the cerebral cortex on DWI was >1.5 cm in diameter or >5 ml in volume. Patients were excluded if there were lesions or artifacts that interfered with image assessments or if acute intracerebral hemorrhage was present. An interpretation of the baseline MRI for eligibility was made by the investigator at the site, but definitive eligibility for the MRI substudy analysis was determined by the MRI Core Laboratory.

Sample Size Determinations

The sample size estimations for this substudy were based on data from a small phase II MRI substudy [19]. Based on these data, a sample size of 44 in each treatment group would provide 80% power to detect a 50% relative difference in the growth of ischemic lesion volume with an α of 0.05 using a two-sided test.

All MRI substudy patients that had two evaluable time points (baseline and month 3) were included in the 'as treated' primary analysis. Any patient that had a baseline MRI but no follow-up MRI (either due to death or lost to follow-up) was excluded from the primary analysis.

Primary Substudy Analysis

A nonparametric analysis of covariance was used for the primary MRI substudy analysis. Ischemic lesion volume and National Institutes of Health stroke scale (NIHSS) score at baseline were used as covariates. An ordinary least-squares regression was fit to the log-transformed ischemic lesion volume at month 3 and NIHSS score at baseline. A Cochran-Mantel-Haenszel correlation statistic was calculated on the ranks of the residuals from the least-squares regression line.

Other Analyses

A secondary analysis included the baseline hypoperfusion volume (as measured by the MTT map) as a covariate. For this analysis, the same nonparametric analysis of covariance was

used as described for the primary analysis. However, in addition to ischemic lesion volume and NIHSS score at baseline, the hypoperfusion volume was used as a covariate.

Another secondary analysis included MRI substudy patients with missing values secondary to death due to stroke. An ordinary least-squares regression was fit to the rank of ischemic lesion volume at month 3 as a function of the ranks of ischemic lesion volume and NIHSS score at baseline. The lowest rank was assigned to patients who did not have ischemic lesion data at month 3 due to death. A Cochran-Mantel-Haenszel correlation statistic was calculated on the residuals from the least-squares regression line.

Descriptive statistics on lesion size, percent diffusion perfusion mismatch ($100 \times (\text{MTT volume} - \text{DWI volume})/\text{DWI volume}$) and volume change were tabulated within and across treatment groups. Spearman rank correlations were calculated to investigate the relationship of lesion volume to scores on clinical scales. In a post hoc analysis, the association of a decrease in lesion volume with an improvement in the National Institutes of Health Stroke Scale (NIHSS) of 7 or more points, which had been observed in another study [13], was assessed by a χ^2 test.

Results

Of 2,171 subjects that were enrolled in the GAIN clinical outcome studies, 390 were enrolled at MRI substudy centers, 181 (46%) of whom were screened with MRI prior to 6 h of stroke onset. Of those, 106 (57 placebo, 48 gavestinel) qualified for the MRI substudy based on acute ischemic lesion size and location. Seventy-one percent, 75/106 had month 3 scans (primary analysis population); 41 treated with placebo, 34 treated with gavestinel. Of the 31 patients excluded from the primary analysis, 25 (24%) died, and 6 (5%) refused follow-up or had technically unusable data. Of the 106 substudy patients, PWI scans were obtained in 100 cases, 95 of which were technically adequate for analysis. For the primary analysis population there were 67 usable baseline PWI scans. The median time from stroke onset to start of the MRI scan was 4.4 h, the median duration of the MRI scanning session was 0.5 h and the median time from the completion of the MRI to the initiation of treatment was 0.5 h. The median time from stroke onset to treatment was 5.7 h.

Of the 209 patients at substudy sites who did not undergo MRI, the reasons for not obtaining the scan were reported by the investigator to be patient related (e.g., MRI contraindication, refusal of consent, medical instability, intracerebral hemorrhage on screening CT) in 83 cases, insufficient time in 55 cases, lack of scanner or MRI staff availability in 53 cases, and other or unstated in 18 cases.

Patient baseline characteristics were not significantly different between the treatment groups and representative of those in the clinical outcome study [7, 10] samples from which they came. Median NIHSS was 15 in either group at baseline. Lesion volumes did not differ between the groups at baseline and at month 3 (tables 1, 2). There was no significant effect of gavestinel on infarct volume in primary and secondary analyses of covariance for the effect of gavestinel on infarct volume. No significant difference was found on clinical outcome measures at month 3 (NIHSS, Barthel Index, modified Rankin Score, mortality) in

this substudy sample. Of the 67 adequate PWI scans, 64 (96%) had perfusion defects on MTT and in 50 (75%) of these cases the volume of the hypoperfusion region exceeded the ischemic lesion on DWI (diffusion-perfusion mismatch) by 20%. Patients with diffusion-perfusion mismatch at baseline had a median 27.8% increase in lesion volume, whereas those without a mismatch had a median decrease of -12.9%, indicative of greater lesion growth in patients with mismatch ($p = 0.05$).

The correlations between lesion volumes and clinical severity are listed in table 3. Moderate but significant correlations were observed between NIHSS and lesion volume at baseline and between month 3 lesion volume and the month 3 clinical outcomes.

In the total sample, there was a significant relationship between lesion volume decrease and an NIHSS improvement by 7 or more points ($p < 0.0001$; $\chi^2 = 13.37$; table 4). The positive predictive value of a lesion volume decrease predicting clinical improvement was 83%.

Discussion

These MRI substudy results do not support a neuroprotective effect of gavestinel in any of the analyses, and are thus concordant with the neutral clinical outcomes previously reported for the gavestinel clinical outcome studies [7, 10]. The reasons that preclinical reductions in infarct volume of gavistene in preclinical models have not been demonstrable in humans are not known. Excessive times to treatment, subtherapeutic doses, limitations of preclinical models to predict clinical response, need to combine neuroprotection with reperfusion therapy, or the possibility that the drug is not neuroprotective in humans cannot be ruled out. Such uncertainties stress the potential value of phase II demonstration of the target biologic effects as the basis of decisions to proceed to phase III trials.

This is the first multicenter acute stroke trial with a 6-hour time window to use DWI and PWI as a pretreatment assessment, and thus supports the feasibility of performing MRI as a baseline screening exam in acute stroke trials. Many centers can rapidly access MRI during a time critical in acute stroke, although they may add time to the pre-treatment screening of patients and may delay the initiation of experimental therapy for an average of 30 min if both CT and MRI are performed prior to initiation of treatment.

MRI with DWI and PWI is an appealing imaging modality for stroke since it provides pre-treatment angiography, perfusion, and lesion volume information during a brief, noninvasive assessment. It has been proposed that positive imaging diagnoses would improve patient selection toward the goal of a more optimal target sample for stroke and that the change in lesion volume could serve as a marker for clinical outcome [3]. The additional biologic homogeneity of imaging-based selection will limit the proportion of eligible patients and thereby recruitment rate, and the need for an imaging outcome risks loss to follow-up due to death, a potential source of bias. Earlier times for follow-up imaging prior to hospital discharge may reduce this loss to follow-up. Nonetheless, the study has demonstrated that within a 6-hour window trial, enrollment on the order of 100 patients is achievable.

These results support the role of lesion volume change measured by MRI as a marker of clinical outcome in stroke trials. The correlations of clinical scales to lesion volumes

replicate prior observations and confirm that MRI measures in the present study performed as expected [12–15]. The relationship of a decrease in lesion volume to clinical improvement over the 3-month period of observation in this trial replicates the same relationship observed in two other stroke trials with a 24-hour treatment time window [13, 16].

The present sample also confirms that lesion growth is greater in patients with a diffusion-perfusion mismatch and supports the hypothesis that mismatch may identify the optimal patient in whom to demonstrate a beneficial effect in lesion growth clinical trials [12, 13, 20–24]. Recent results have given more direct support. The Desmoteplase in Acute Stroke trial, a randomized control trial of a thrombolytic drug up to 9 h after stroke onset and selecting only patients with a diffusion-perfusion mismatch, found significant benefit on both the target imaging outcome, early reperfusion, and 90-day clinical outcome [25].

DWI and PWI are a more direct and objective measure of ischemic pathology than clinical rating scales, and may provide a direct measure of tissue salvage in stroke therapy. MRI not only has a role in identifying and verifying acute ischemic pathology, but it can be a powerful tool in proof of principle phase II dose selection clinical trials by providing evidence of target physiological response in sample sizes too small to demonstrate clinical benefits. Although reduction of infarct volume is considered a necessary condition mediating therapeutic neuroprotection in stroke, it is not sufficient to conclude efficacy in stroke patients. A statistically significant reduction in lesion volume could be too small to translate into a clinically significant benefit, or toxicity could negate clinical benefits attributable to smaller infarcts. Infarct reduction, while evidencing the target biological effect of neuroprotective therapy, must also be accompanied by clinical benefits to claim efficacy for a drug. The hypothesis that MRI measurements of ischemic pathology may be a surrogate marker for clinical benefits at phase III will require validation from future clinical trials that find concordance of clinical and imaging outcome with both effective and ineffective therapies.

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Appendix

Contributing Centers

The following is a list of centers by country and local principal investigator, who contributed patients to the GAIN MRI substudy.

Australia: S. Davis, J. Frayne, P. Talman; *Belgium:* W. Robberecht; *Canada:* S. Black, V. Hachinski; *Germany:* K. Einhaeupl, G. Hamann, D. Schneider, M. Siebler, C. Weiller;

Finland: M. Kaste, J. Sivenius; *France:* F. Chollet, D. Leys, J.-M. Orgogozo; *Puerto Rico:* J. Moreira; *Singapore:* V. Ramani, C. Chen; *Sweden:* O. Skogar, P. Wester; *United States:* J. Brillman, C. Chaves, D. Chiu, W. Clark, B. Coull, T. Devlin, G. Graham, K. Johnston, D. Hill, C. Hsu, T.-L. Hwang, M. Kaminski, D. Kaufman, S. Nazarian, G. Newman, S. Sen, S. Tuhim, D. Wang, G. Zoarski.

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Table 1

Ischemic lesion volumes in the primary analysis sample

	Baseline lesion, ml	Month 3 lesion, ml	Lesion volume change, %
Placebo (n = 41)			
Mean	61.0	74.3	45.5
SD	75.7	88.6	170.3
Median	40.8	54.3	22.9
Gavestinel (n = 34)			
Mean	64.0	87.3	40.4
SD	69.0	95.2	152.6
Median	40.1	49.2	2.3
All patients (n = 75)			
Mean	62.4	80.2	43.2
SD	72.3	91.3	161.5
Median	40.8	49.3	20.1

Table 2

Ischemic lesion and hypoperfusion volumes in patients with PWI performed

	Baseline lesion, ml	Baseline hypoperfusion ml	Month 3 lesion ml	Lesion volume change, %
DWI-PWI mismatch (n = 50)				
Mean	57.2	188.0	77.0	63.6
SD	60.1	108.3	80.5	87.7
Median	42.1	197.0	54.6	27.8
No DWI-PWI mismatch (n = 17)				
Mean	90.4	74.6	99.8	-6.7
SD	107.3	97.2	127.1	-46.7
Median	40.1	39.0	26.7	-12.9
All patients (n = 67)				
Mean	65.6	159.2	82.8	45.8
SD	75.4	116.0	93.9	66.8
Median	40.8	160.9	49.3	20.8

Table 3

Correlation of clinical scales to lesion volumes

Comparison	n	Correlation
Baseline NIHSS:baseline lesion volume	106	0.54
Month 3 NIHSS:month 3 lesion	76	0.72
Month 3 Rankin:month 3 lesion	76	0.61
Month 3 Barthel:month 3 lesion	76	−0.62

All correlations significant at $p < 0.001$.

Table 4

Relationship of lesion volume decrease to clinical improvement over 3 months

	NIHSS improvement	
	yes	no
Volume decrease		
Yes	25	5
No	17	28

 $\chi^2 = 15.16$; $p < 0.0001$; $\phi^2 = 0.20$.