

Pilot Study of Intravenous Glyburide in Patients With a Large Ischemic Stroke

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Background and Purpose—Preclinical and retrospective clinical data indicate that glyburide, a selective inhibitor of sulfonylurea receptor 1-transient receptor potential melastatin 4, is effective in preventing edema and improving outcome after focal ischemia. We assessed the feasibility of recruiting and treating patients with severe stroke while obtaining preliminary information on the safety and tolerability of RP-1127 (glyburide for injection).

Methods—We studied 10 patients with acute ischemic stroke, with baseline diffusion-weighted imaging lesion volumes of 82 to 210 cm³, whether treated with intravenous recombinant tissue-type plasminogen activator, age 18 to 80 years, and time to RP-1127 ≤10 hours.

Results—Recruitment was completed within 10 months. The mean age was 50.5 years, and baseline diffusion-weighted image lesion volume was 102±23 cm³. There were no serious adverse events related to drug and no symptomatic hypoglycemia. The increase in ipsilateral hemisphere volume was 50±33 cm³. The proportion of 90-day modified Rankin Scale ≤4 was 90% (40% modified Rankin Scale, ≤3).

Conclusions—RP-1127 at a dose of 3 mg/d was well tolerated and did not require any dose reductions. A clinical trial of RP-1127 is feasible.

Clinical Trial Registration—URL: <http://www.clinicaltrials.gov>. Unique identifier: NCT01268683. (*Stroke*. 2014;45:281-283.)

Key Words: acute treatment ■ brain swelling ■ cerebral edema ■ glyburide ■ hemorrhagic transformation ■ ischemic stroke

The recently characterized ion channel composed of sulfonylurea receptor 1 and transient receptor potential melastatin 4¹ is a promising therapeutic target in stroke. The channel is upregulated in all cell types of the neurovascular unit after ischemia.¹ Excessive channel opening leads to the influx of sodium and water, oncotic cell swelling, and necrotic cell death.² Preclinical studies have shown that pharmacological blockade using a low dose of the selective sulfonylurea receptor 1 inhibitor, glyburide, reduces infarct volume, reduces mortality, and improves neurological outcomes.^{1,3,4}

Here, we report on a pilot study of RP-1127 (glyburide for injection) in patients with severe ischemic stroke who were at

high risk for developing clinically significant brain swelling (Glyburide Advantage in Malignant Edema and Stroke-Pilot).

Methods

Approval for this study was obtained from local institutional review boards. Patient surrogates provided written informed consent. This study was a prospective, open-label, multicenter, phase IIa clinical trial of RP-1127. The primary outcomes of feasibility were (1) the rate of recruitment; (2) proportion of patients recruited versus screened; (3) the ability to manage blood glucose levels according to protocol. The secondary objectives were to obtain preliminary data on safety and tolerability of RP-1127 and to compare clinical and imaging outcome data with historical controls.⁵ The primary safety outcomes were

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Table 1. Baseline Demographic and Clinical Characteristics

	n=10
Age, mean±SD (min–max)	50.5±15.3 (25–73)
Men % (n)	30% (3)
Nonhispanic whites % (n)	30% (3)
Baseline NIHSS, median±IQR (min–max)	18±8 (11–31)
History % (n)	
Arterial hypertension	50% (5)
Diabetes mellitus	20% (2)
Prior ischemic stroke	40% (4)
Atrial fibrillation	10% (1)
Intravenous thrombolysis	90% (9)
Left hemisphere	60% (6)
Laboratory values, mean±SD (min–max)	
Hemoglobin, g/dL	12.5±3.7 (5.1–16.6)
Blood glucose, mg/dL	125.6±31 (98–207)
Creatinine, mg/dL	1.0±0.4 (0.6–1.7)
Time from onset to start of RP-1127 infusion, h; mean±SD (min–max)	8.7±1.2 (6.8–9.9)
Time to MRI, h; mean±SD (min–max)	5.3±1.9 (2.2–7.5)
Vessel occlusion	
Cervical carotid occlusion	30% (3)
Middle cerebral artery (M1 segment)	70% (7)
Middle cerebral artery (M2 segment)	30% (3)
Anterior cerebral artery	0% (0)

All values expressed in % (n) except where otherwise indicated. IQR indicates interquartile range; and NIHSS, National Institutes of Health Stroke Scale.

all-cause deaths, hemorrhagic events, and hypoglycemia. The protocol included prespecified rules for reducing or discontinuing study drug because of hypoglycemia, hemolytic anemia, and liver or cardiac toxicity (additional details in the online-only Data Supplement).

Inclusion criteria were baseline diffusion-weighted image lesion volume, 82 to 210 cm³; age 18 to 80 years; time from symptom onset to start of study drug infusion ≤10 hours.

Results

Between February 2011 and May 2012, 10 subjects were enrolled and treated at University of Maryland and the Massachusetts General Hospital within 9.6 months, which was faster than the anticipated time of 14 months, based on an a priori review of the local stroke registries using the proposed

inclusion/exclusion criteria. The baseline characteristics of enrolled subjects are presented in Table 1. Recombinant tissue-type plasminogen activator was administered to 5 subjects within 0 to 3 hours and to 4 subjects from 3 to 4.5 hours.

Two subjects experienced serious adverse events during hospitalization. One patient required decompressive craniectomy and survived; another patient required decompressive craniectomy and died. In both cases, neurological deterioration was considered to be unrelated to the study drug.

Hypoglycemia was predefined as a blood glucose <70 mg/dL. There were no instances of hypoglycemia that triggered a reduction in dose or cessation of study drug infusion.

At 90 days, 90% of patients had modified Rankin Scale ≤4, and 40% had modified Rankin Scale ≤3. There were no PH1/PH2 hemorrhages. Baseline and follow-up neuroimaging metrics are shown in Table 2. The mean (±SD) increase in ipsilateral hemisphere volume (change from baseline to day 3 or last visit) was 50±33 cm³, and the mean diffusion-weighted image lesion volume increase was 60±41 cm³.

Discussion

The present study examined a potential pharmacotherapy for the prevention of edema after ischemia in humans. The main finding of this study is that our protocol for administering RP-1127 to critically ill patients with stroke is feasible. No safety concerns, hypoglycemia, or drug-related serious adverse events were observed. Declines in serum glucose were similar to those in prior natural history and glucose control studies.⁶

Because of the morbidity and mortality that are a direct consequence of brain swelling after stroke, there is an urgent need to identify novel treatments to ameliorate edema formation. Our inclusion criteria were developed to enroll patients to test the major potential therapeutic mechanism of glyburide, namely prevention of edema. The diffusion-weighted image cutpoint of 82 cm³ has been prospectively validated in an independent cohort.⁵ Because our approach aimed to establish proof of principle, we targeted subjects using this highly predictive marker of swelling.

The subjects in this pilot study had increases in hemisphere volumes >3 days of 50±33 cm³ compared with 72±27 cm³ in historical controls.⁷ The diffusion-weighted image lesion volume increase was 60±41 cm³ compared with 96±41 cm³ in historical controls.⁷ Even though 90% of subjects presented with high National Institutes of Health Stroke Scale scores and received intravenous recombinant tissue-type plasminogen activator, there were no PH1/PH2 hemorrhages, consistent with a

Table 2. Centrally Determined Neuroimaging Lesion Volumes

	GAMES-Pilot (n=10)	
	Mean (SD)	95% CI
Mean hemisphere volume, baseline, cm ³ (SD)	468.2 (73.7)	(420.1, 516.3)
Mean hemisphere volume, final visit, cm ³ (SD)	507.9 (59.2)	(469.2, 546.6)
Mean hemisphere volume increase, cm ³ (SD)	49.9 (33.3)	(29.3, 70.5)
Mean DWI volume, baseline, cm ³ (SD)	101.8 (22.6)	(87.0, 116.6)
Mean DWI volume, final visit, cm ³ (SD)	160.4 (51.7)	(126.6, 194.2)
Mean DWI volume increase, cm ³ (SD)	60.3 (41.4)	(34.6, 86.0)

CI indicates confidence interval; DWI, diffusion-weighted image; and GAMES, Glyburide Advantage in Malignant Edema and Stroke.

retrospective study of stroke in patients with diabetes mellitus treated with oral sulfonylureas.⁸ The proportion of subjects with 90-day modified Rankin Scale ≤ 4 was 90% compared with 24% (at 12 months) in patients from a pooled analysis of decompressive craniectomy trials.⁹

This pilot study has shortcomings. It was open-label, had no placebo control arm, and the number of patients studied was small. Therefore, we cannot determine whether any seemingly favorable clinical outcome was because of RP-1127, enrollment of patients with milder stroke, or some other cause. However, the reduced hemispheric volume, hemorrhagic transformation, lesion growth, mortality, and improved neurological outcomes observed in this pilot study parallel findings in preclinical studies.^{1,3,4}

Further clinical investigation is warranted to determine whether RP-1127 can mitigate the devastating consequences associated with severe anterior circulation infarction and resulting edema.

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The sponsor for this study was Remedy Pharmaceuticals, Inc.

Disclosures

The study PI (Dr Sheth) made all decisions on analysis and publication and assumes responsibility for the article. Drs Sheth and Kimberly received per patient reimbursement for enrollment into Glyburide Advantage in Malignant Edema and Stroke-Pilot.

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Supplemental Methods

The secondary objectives were to assess the safety and tolerability of RP-1127, and to compare clinical and imaging outcome data with historical controls.¹ To assess the feasibility of recruitment and of the protocol procedures, a sample size of 10 patients was selected. No interim analyses were planned. Safety data was reviewed by the medical monitor. The protocol included pre-specified rules for reducing or discontinuing study drug due to hypoglycemia, hemolytic anemia, and liver or cardiac toxicity. Tolerability was assessed by the proportion of patients requiring reduction or discontinuation per protocol.

Exclusion criteria included the use of endovascular therapy and known sulfonylurea treatment in the prior 30 days. DWI infarct volume assessment was made in real time using the ABC/2 method.²

All subjects enrolled in GAMES-Pilot received a 0.13 mg IV bolus of RP-1127 over 2 minutes, followed by approximately 3 mg/day IV drug infusion for 72 hours. The RP-1127 dose (3 mg/day) in GAMES Pilot was the maximum tolerated dose from the Phase I study in healthy patients. The 3 mg/day dose resulted in no difference in incidence of blood glucose (BG) levels below 70 mg/dL compared to placebo. One subject at the 3 mg/day dose experienced a peak glyburide plasma level at one time point of 50.7 ng/mL. Glyburide plasma levels of 59 ng/mL were associated with BG levels below 70 mg/dL at doses of 6 and 10 mg/day. Unpublished data from Dr. Simard's laboratory show that the glyburide dosing regimen in rats of 400 ng/hour subcutaneously, an effective dose twice that used in published preclinical studies (to improve the fidelity of detecting low serum concentrations), results in average steady-state plasma glyburide levels of 16 ng/mL, without significant hypoglycemia. Therefore, the rationale was that the dose in the GAMES Pilot study would result in plasma levels in humans that exceed the highly effective therapeutic dose in rats.

Frequent blood glucose measurements were performed. Multicenter clinical guidelines were developed that standardized decompressive craniectomy (DC), osmotherapy and other critical care interventions.

Subjects underwent baseline and follow up magnetic resonance imaging (MRI) at 24, 48 and 72 hours. DWI and hemisphere lesion volumes were measured using standard planimetric software (Analyze 9.0; Biomedical Imaging Resource, Mayo Clinic, Rochester, MN).³ Hemorrhage determination was made using the ECASS classification.⁴ A central certified research nurse performed all 30- and 90-day telephone assessments of the modified Rankin Scale (mRS) scores ⁵

Descriptive statistics were used to summarize all evaluable data. For the imaging measurements, the final follow-up scan was defined as the last evaluable scan collected at 72 hours or prior to DC. One subject required DC prior to the collection of any follow-up MRI; the mean increase in hemisphere volume and DWI for this subject was imputed from the worst observed change amongst the subjects. Pre-specified outcomes targets were: (1) the percentage that achieved mRS 0-4 without DC; (2) no increase in mortality compared to historical series.

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