NEW INSIGHTS INTO BRAIN SWELLING AFTER STROKE

W Taylor Kimberly MD PhD
6 May 2013
OBJECTIVES

• Background: introduction to stroke

• Mechanism: types of cerebral edema

• Specific target: preclinical data on the SUR1-TRPM4 channel

• Clinical data: Results of the GAMES-Pilot Trial

• Edema mechanisms: GAMES-Pilot imaging and plasma biomarkers

• Next steps: GAMES-RP
BACKGROUND

- 800,000 strokes occur each year
- 4th leading cause of death in the United States
- Leading cause of long-term disability
- Estimated direct and indirect costs of ~$75 billion
- Two types of strokes:
  - blockage of blood flow: ischemic
  - bleeding from a blood vessel: hemorrhagic
Cerebral Blood Vessels
BACKGROUND

Cerebrovascular Territories

Right

Left

Middle Cerebral Artery (Coronal Plane)

Cortical vascular territories

- Anterior cerebral artery
- Middle cerebral artery
- Posterior cerebral artery

anterior  middle  posterior
BACKGROUND

Ischemic Stroke:
Cerebrovascular Blockage
BACKGROUND

Left Middle Cerebral Artery (MCA) Stroke

- Word-finding difficulty (aphasia)
- Right-sided weakness
- Right-sided sensory loss
- Right visual field defect
- Left gaze deviation
- Slurred speech (dysarthria)
- Difficulty reading, writing, or calculating

MY FLAM JUST SLAPPED THE GROO. DIDN’T GRINGLE AT ALL!
Left Middle Cerebral Artery (MCA) Stroke

- Left-sided sensory loss
- Inattention (neglect)
- Unawareness of deficits
- Left sided weakness
- Left visual field defect
- Right gaze deviation
- Slurred speech (dysarthria)
An increasing NIHSS number corresponds to a worse neurological deficit and more severe stroke.
For patients with suspected stroke, patients should bypass hospitals that do not have resources to treat stroke and go to a facility capable of treating acute stroke.

Teleneurology has increased the number of point-of-care centers that can receive, evaluate, and treat patients with suspected acute stroke.
BACKGROUND

IV thrombolysis

- Symptoms within 3h (4.5 with consent)
- Ischemic stroke not well-defined on CT
- INR < 1.8, Plt > 100k
- No recent surgery or hemorrhage (14d/21d)
- No recent stroke
- No history of SAH or ICH
- SBP < 185 (can be treated)
- NIHSS > 4
**BACKGROUND**

**Endovascular Therapy**

- Multiple techniques available
  - Intra-arterial tPA/urokinase
  - MERCI/Penumbra
  - Stentrievers (Solitaire/Trevo)

- Efficacy data is inconclusive (IMS-3 negative)

- Considered for stroke < 6 hours anterior circulation, < 12-24 hours posterior circulation with confirmation of vessel cutoff
OBJECTIVES

• Background: introduction to stroke
  • Mainstay of treatment since 1996 is “revascularization”
  • Mechanism: types of cerebral edema

• Specific target: preclinical data on the SUR1-TRPM4 channel

• Clinical data: Results of the GAMES-Pilot Trial

• Edema mechanisms: GAMES-Pilot imaging and plasma biomarkers

• Next steps: GAMES-RP
OBJECTIVES

• Background: introduction to stroke

• Mechanism: types of cerebral edema
  • An alternative therapeutic target

• Specific target: preclinical data on the SUR1-TRPM4 channel

• Clinical data: Results of the GAMES-Pilot Trial

• Edema mechanisms: GAMES-Pilot imaging and plasma biomarkers

• Next steps: GAMES-RP
Brain Edema results from:

1. **Cytotoxic edema**
   cytotoxic injury causes cellular swelling

2. **Vasogenic edema**
   vasogenic injury causes dysfunction of the BBB

   - **osmotic forces:** ion concentration gradients
   - **hydrostatic forces:** vascular pressure gradients
Cytotoxic edema

- rapid redistribution of water into cells
- no net change in total water
- basis for DWI acute stroke imaging
**VASOGENIC CEREBRAL EDEMA**

**Vasogenic edema: ionic forces**
- net movement of ions into the brain
- increase in total water content
- contributes to brain swelling
Vasogenic edema: hydrostatic forces

- Breakdown of the BBB
- Hydrostatic pressure forces plasma into the brain
- Severe BBB injury leads to hemorrhagic transformation
OBJECTIVES

• Background: introduction to stroke

• Mechanism: types of cerebral edema

• Specific target: preclinical data on the SUR1-TRPM4 channel

• Clinical data: Results of the GAMES-Pilot Trial

• Edema mechanisms: GAMES-Pilot imaging and plasma biomarkers

• Next steps: GAMES-RP
PRECLINICAL DATA

• SUR1 and TRPM4 are only present in the CNS after injury.
• TRPM4 is a calcium-activated non-selective channel that allows cations into the cell and water follows passively.
• An analogous channel exists in the pancreas and regulates insulin secretion.
SUR1-TRPM4 CHANNEL OPENING CAUSES CYTOTOXIC EDEMA

A. Control depletion
B. ATP depletion 5 min
C. ATP 25 min

Courtesy of M. Simard
GLYBURIDE REDUCES MORTALITY AND SWELLING IN A RAT MCAO MODEL
OBJECTIVES

- Background: introduction to stroke
- Mechanism: types of cerebral edema
- Specific target: preclinical data on the SUR1-TRPM4 channel
- Clinical data: Results of the GAMES-Pilot Trial
- Edema mechanisms: GAMES-Pilot imaging and plasma biomarkers
- Next steps: GAMES-RP
Phase 2a open label trial of RP-1127 (glyburide for injection) at 2 centers (UMMC and MGH)

Baseline MRI infarct volume of >82cc on DWI

72 hour infusion for patients within 10 hours at ~3 mg/day

Daily MRI at 24, 48 and 72 hours, with frequent PK sampling

Modified Rankin Scale outcome assessment at 30 and 90 days
GAMES-PILOT vs. HISTORICAL CONTROLS

Imaging Outcomes

Baseline DWI

72 hr DWI

Historical Control

RP-1127
## GAMES-PILOT vs. HISTORICAL CONTROLS

### Imaging Outcomes

<table>
<thead>
<tr>
<th></th>
<th>GAMES-Pilot (n=10)</th>
<th>Subset of EPITHET (n=12)</th>
<th>Two-sided p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean hemisphere volume, baseline, cm³ (SD)</strong></td>
<td>468.2 (73.7) (420.1, 516.3)</td>
<td>460.3 (62.7) (424.8, 495.8)</td>
<td>0.79</td>
</tr>
<tr>
<td><strong>Mean hemisphere volume, final visit, cm³ (SD)</strong></td>
<td>507.9 (59.2) (469.2, 546.6)</td>
<td>531.8 (59.6) (498.1, 565.5)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Mean hemisphere volume increase, cm³ (SD)</strong></td>
<td>49.9 (33.3) (29.3, 70.5)</td>
<td>71.5 (27.0) (56.2, 86.8)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Mean DWI volume, baseline, cm³ (SD)</strong></td>
<td>101.8 (22.6) (87.0, 116.6)</td>
<td>137.7 (33.8) (118.6, 156.8)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Mean DWI volume, final visit, cm³ (SD)</strong></td>
<td>160.4 (51.7) (126.6, 194.2)</td>
<td>233.8 (41.5) (210.3, 257.3)</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Mean DWI volume increase, cm³ (SD)</strong></td>
<td>60.3 (41.4) (34.6, 86.0)</td>
<td>96.1 (40.4) (73.3, 118.9)</td>
<td>0.05</td>
</tr>
</tbody>
</table>
## GAMES-PILOT vs. HISTORICAL CONTROLS

### Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>GAMES-Pilot</th>
<th>Propensity-matched EPITHET-MMI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>9</td>
<td>15</td>
<td>0.55</td>
</tr>
<tr>
<td>Med NIHSS</td>
<td>19.0</td>
<td>19.0</td>
<td>0.55</td>
</tr>
<tr>
<td>Age</td>
<td>51.6 ± 15.8</td>
<td>68.7 ± 14.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Glucose</td>
<td>128 ± 32</td>
<td>126 ± 27</td>
<td>0.91</td>
</tr>
<tr>
<td>DWI</td>
<td>102 ± 24</td>
<td>66 ± 32</td>
<td>0.01</td>
</tr>
<tr>
<td>mRS 0-1</td>
<td>0% (0)</td>
<td>0% (0)</td>
<td>1.00</td>
</tr>
<tr>
<td>mRS 0-2</td>
<td>11.1% (1)</td>
<td>6.7% (1)</td>
<td>1.00</td>
</tr>
<tr>
<td>mRS 0-3</td>
<td>44.4% (4)</td>
<td>20.0% (3)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>mRS 0-4</strong></td>
<td><strong>100% (9)</strong></td>
<td><strong>46.7% (7)</strong></td>
<td><strong>0.01</strong></td>
</tr>
<tr>
<td>mRS 0-5</td>
<td>100% (9)</td>
<td>73.3% (11)</td>
<td>0.29</td>
</tr>
<tr>
<td>Mortality</td>
<td>0% (0)</td>
<td>26.7% (4)</td>
<td>0.26</td>
</tr>
<tr>
<td>Symptomatic Hemorrhage</td>
<td>0% (0)</td>
<td>13.3% (2)</td>
<td>0.51</td>
</tr>
</tbody>
</table>
OBJECTIVES

• Background: introduction to stroke

• Mechanism: types of cerebral edema

• Specific target: preclinical data on the SUR1-TRPM4 channel

• Clinical data: Results of the GAMES-Pilot Trial

• Edema mechanisms: GAMES-Pilot imaging and plasma biomarkers

• Next steps: GAMES-RP
Identification of intermediate endpoints that:

- Strengthen the clinical findings
- Support mechanism of action of the drug
- Provide insight into the biology of cerebral edema
- Analysis of both imaging and plasma biomarkers
**IMAGING CYTOTOXIC EDEMA**

Apparent Diffusion Coefficient (ADC) MRI detects cytotoxic edema

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Day 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control</td>
<td><img src="image1" alt="Control Baseline" /></td>
<td><img src="image2" alt="Control Day 1" /></td>
</tr>
<tr>
<td>ADC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>GAMES</td>
<td><img src="image3" alt="GAMES Baseline" /></td>
<td><img src="image4" alt="GAMES Day 1" /></td>
</tr>
</tbody>
</table>

→ IV glyburide does not appear to alter cytotoxic edema in patients
T2 FLAIR MRI detects vasogenic edema

- 24 hours
- 48 hours
- 72 hours
IMAGING VASOGENIC EDEMA

Day 2

Control

GAMES

DWI

FLAIR
T2 FLAIR MRI detects vasogenic edema

***, p<0.005
IMAGING VASOGENIC EDEMA

T2 FLAIR MRI detects vasogenic edema

***, p<0.01
There is increased water diffusion after day 1, from the entry of edema fluid into the brain.
MMP-9 is a marker of BBB integrity and vasogenic edema.
Imaging and plasma biomarkers and vasogenic edema

**Imaging analysis:**

- glyburide appears to attenuate vasogenic edema
- imaging data alone does not distinguish between ionic edema or hydrostatic edema

**Plasma analysis:**

- MMP-9 identifies a biological pathway
- relates drug mechanism of action to BBB physical integrity (ie, hydrostatic edema)
OBJECTIVES

• Background: introduction to stroke

• Mechanism: types of cerebral edema

• Specific target: preclinical data on the SUR1-TRPM4 channel

• Clinical data: Results of the GAMES-Pilot Trial

• Edema mechanisms: GAMES-Pilot imaging and plasma biomarkers

• Next steps: GAMES-RP
GAMES-RP TRIAL

- 10 US Centers, up to a maximum of ~15 sites
- Randomized, double-blind, placebo-controlled phase II trial
- Two-stage, adaptive design with an interim analysis after the first 50 patients
- Second stage will proceed after review by unblinded statistician and DSMB. If a pre-specified futility threshold is not met, recalculate sample size estimate up to a maximum of 190 additional subjects.
• **Primary safety endpoint:** refractory hypoglycemia

• **Primary efficacy endpoint:** 20% difference in the proportion of modified Rankin Scale score 0-4 + decompressive craniectomy (DC)
GAMES-RP TRIAL

- Baseline MRI infarct volume of >82cc on diffusion imaging in patients with or without IV tPA
- 72 hour infusion for patients within 10 hours at 3 mg/day
- One study-related brain MRI after drug infusion at 72-84 hours
- PK and biomarker sampling at 5 time points
- DNA collection for consenting patients
GAMES-RP TRIAL

**Study Leadership**
Kevin Sheth  
W. Taylor Kimberly

**Sponsor**
Sven Jacobson  
Remedy Pharmaceuticals

**Data coordinating center**
Jordan Elm (MUSC)

**Imaging coordinating center**
Lauren Beslow-Kaye  
Gordon Sze (Yale)

**Biomarker coordinating center**
Mass General Hospital

**DSMB**
Don Easton  
Karen Johnston  
Michael Diringer

**Adjudication**
Rudiger von Kummer  
Javier Romero  
Andrew Demchuk
ACKNOWLEDGEMENTS
GAMES-PILOT and GAMES-RP

**U Maryland**
Kevin Sheth
Barney Stern
J. Marc Simard

**Remedy Pharmaceuticals, Inc**
Sven Jacobson

**Data Coordinating Center**
Jordan Elm

**Mass General Hospital**
Sydney O’Connor
Hannah Irvine
Bart Brouwers
Matt Siket
J. Alfredo Caceres
Octavio Pontes Neto
Neuro ICU Nurses

**Imaging Coordinating Center**
Albert Yoo
ACKNOWLEDGEMENTS

BIOMARKER ANALYSIS

**Imaging analysis**
Tom Battey
Ruchi Jha
Ona Wu

**Plasma analysis**
Ly Pham
Yu Wang

**Genetics**
Guido Falcone
Chris Anderson
Billy Devan
Jonathan Rosand

**Collaborators**
Aneesh Singhal
Karen Furie
Thank you