Cutting Edge Therapies for Acute Stroke Patients in CT

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Disclosures

• Co-PI of Yale NIH Funded Neurology Emergency Treatment Trials (NETT) Network - Spoke
• Co-PI of Phase II Study of RP-1127 in Patients at High Risk for Malignant Infarction - GAMES-RP

Outline

What can a tertiary care medical center like Yale-New Haven Hospital offer acute stroke patients at outlying community facilities?

A Neurovascular Research Center focused on …
Stroke Research

- Ischemic Stroke Studies
  - Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP)
  - Intravascular Cooling in the Treatment of Stroke (ICTuS 2/3)
  - Platelet Oriented Inhibition in New TIA and Minor Stroke (POINT)

- Hemorrhagic Stroke Studies
  - Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH II)
  - Hi Dose Deferoxamine in Intracerebral Hemorrhage (Hi-Def)
  - Clot Lysis to Enhance and Accelerate Resolution of IVH (CLEAR III)

Neurology Emergency Treatment Trials (NETT)

NETT Mission and Goals

Mission
To improve the outcome of patients with acute neurological diseases of the brain, spinal cord, and peripheral nervous system

Goals
To focus on the emergent phase of patient care
To conduct multiple, large, Phase III clinical trials
Take Home Points

- You are the gatekeepers and provide the opportunity for stroke patients who often have no other treatment options.
- Revascularization therapies are limited by time.
- The treatment window may be longer than we think!
- We now have potentially new treatment options for patients that otherwise have none.
- For patients that present to your hospital within 12 hours of symptom onset with focal deficits … think research!

Yale’s Acute Neurovascular Program

- Collaborations with Emergency Medicine and Emergency Medical Services
- 7 stroke faculty, 6 neuro-critical care faculty
- Accredited fellowships in both programs
- Full time research staff with extensive experience
- Advanced practice teams
- And many, many more!

YNHH: Y-ACCESS line

Y-ACCESS
1-888-964-4233
1-203-688-4788
**Malignant Infarction**

71 yo w/ right MCA syndrome, NIHSS ~20, s/p IV tPA

**Day 1**

**Day 3**

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**Decompressive Craniectomy**


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**Ischemic Stroke Studies**

Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP)

Intravascular Cooling in the Treatment of Stroke (ICTuS 2/3)

Platelet Oriented Inhibition in New TIA and Minor Stroke (POINT)
GAMES

Stroke

Pilot Study of Intravenous Glyburide in Patients With a Large Ischemic Stroke:
Kevin N. Sills, W. Taylor Randwyl, Joseph J. Elia, Thomas A. Kunt, Dikshana M Modica,
Albert J. Yoo, Goya Hasenlila, Bruce Campbell, Geoffrey A. Durell, Norharn M. Devr,
Gregory W. Albers, Wvan Baeckle, J. Max Sauer and Barry J. Menn

Sample Patient

52 yo w/ R MCA occlusion, NIHSS 23, s/p IV tPA

Baseline 72 hours later

GAMES-RP

- Phase II double-blind randomized trial
- 15 US centers
- 50 patients total (25/group) randomized 1:1 for interim analysis
- Primary efficacy endpoint:
  - modified Rankin $\leq$ 4 without decompressive craniectomy
- Primary safety endpoint
  - Hypoglycemina
- Neuroimaging Core - Yale
**GAMES-RP Inclusion Criteria**

- Age 18-80 years
- Clinical diagnosis of ischemic stroke
- Baseline stroke volume of 82 cc by MRI
- Administration of IV tPA up to 4.5 hours permitted but not required
- Start of drug infusion up to 10 hours from symptom onset

**Ischemic Stroke Studies**

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**ICTuS 2/3**

- Hypothermia has been a proven strategy and is now the standard of care for the treatment of cardiac arrest.
- The primary benefit is directed towards neurological outcome.
- Is there any evidence for hypothermia in acute stroke?
Purpose
• To determine whether the combination of thrombolysis and hypothermia is superior to thrombolysis alone for the treatment of acute ischemic stroke

Study Population
• Age 22-82
• Acute ischemic stroke patients
• IV tPA within 3 hours of symptom onset
• NIHSS ≥7 & ≤20 (right hemisphere)
• ≥7 & ≤24 (left hemisphere)
• Pre-stroke mRS 0-1

Ischemic Stroke Studies

- Glyburide Advantage in Malignant Edema and Stroke (GAMES-RP)
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Question
• In patients receiving aspirin 81-325 mg/day, is additional treatment with clopidogrel (Plavix®) 75 mg/day (after a loading dose of 600 mg) effective?

Endpoint
• Preventing major ischemic vascular events (ischemic stroke, myocardial infarction, and ischemic vascular death) at 90 days after a TIA or minor stroke

What is a “minor” stroke?

POINT

• Prospective, randomized, double-blind, multicenter trial, with about 150 participating sites and 4,150 subjects
• The risk of another stroke occurring after a TIA or minor stroke is high.
• Platelet aggregation, or clumping which can cause clotting, is an important contributing factor in cerebral ischemia.
• Until recently, the combination of Plavix and aspirin had never been tested as an acute ischemic stroke therapy

POINT Inclusion Criteria

• No intravenous or intra-arterial thrombolysis
• No history of spontaneous ICH
• Main inclusion criteria is enrollment within 12 hours of mild stroke or TIA as assessed by ABCD² score
Day 1 Loading Dose:

- Administer loading dose (8 study tablets) within 2 hours of randomization in the presence of research team member
- Administer first dose of aspirin (81-350 mg) at the discretion of treating physician.
  - Strongly recommended dose: 162 mg daily x 5 days followed by 81 mg daily

Days 2-90:
- 1 pill of study drug or placebo
- 1 prescribed dose of 81-325 mg aspirin daily

Hemorrhagic Stroke Studies

**Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH II)**

- Hi Dose Deferoxamine in Intracerebral Hemorrhage (Hi-Def)
- Clot Lysis to Enhance and Accelerate Resolution of IVH (CLEAR III)

Background

- ATACH-1 tested three different blood pressure targets to assess for safety. All were safe.
- The Eastern Hemisphere study INTERACT suggested a possible benefit to early BP control but hematoma expansion was not limited.
ATACH-II

Primary Study Objectives

• BP <140 vs <180 mmHg

• To determine the therapeutic benefit of intensive SBP treatment (SBP < 140 mmHg) compared with standard SBP treatment (SBP < 180 mmHg)

• Goal is to reduce the percentage of patients with death and disability (mRS of 4 – 6) at 90 days among subjects with ICH treated within 4.5 hours of symptom onset

ATACH-II Inclusion Criteria

• Age 18 years or older

• IV nicardipine can be initiated within 4.5 hours

• Total GCS score of 5 or greater at time of ED arrival

• CT scan demonstrates intra-parenchymal hematoma with hematoma volume measurement <60 cc

• INR value < 1.5

ATACH-II

• For subjects randomized prior to infusion
  – SBP >180 mmHg prior to antihypertensive treatment (this includes pre-hospital treatment)
  – WITHOUT spontaneous SBP reduction to < 180 mmHg at the time of randomization

• For subjects randomized after antihypertensive administration
  – Admission SBP >180 mmHg prior to IV antihypertensive treatment (this includes pre-hospital treatment)
  – WITHOUT SBP reduction to below 140 mmHg at the time of randomization
Nicardipine IV * should be started according to patient need, and may be started prior to randomization into ATACH-II.

<table>
<thead>
<tr>
<th>Starting Dose</th>
<th>Increase by</th>
<th>Maximum Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicardipine</td>
<td>5 mg/hr</td>
<td>15 mg/hr</td>
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<tr>
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<td>2.5 mg/hr</td>
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Hemorrhagic Stroke Studies

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II)
- Hi Dose Deferoxamine in Intracerebral Hemorrhage (Hi-Def)
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Hi-Def: Background

Neuronal injury in ICH is not only related to direct tissue damage & hematoma expansion.

There is a need to find novel, safe, and effective neuroprotective strategies to target the secondary effects of ICH to limit brain injury and improve outcome.

Hi-Def

Primary Study Objectives:
- To assess whether it is futile to move DFO (deferoxamine mesylate) forward as a therapeutic intervention for ICH into Phase III evaluation
- We will comparing the outcome of DFO-treated subjects to placebo-treated subjects with respect to good outcome (defined as mRS 0-2 at 90 days) in a futility analysis.
Hi-Def

Additional Analyses:
• Explore the differences between early (≤12h) and late (>12h-to-24h) time windows in DFO treatment effect on functional outcome
• Perform a dichotomized analysis considering the percentage of DFO- and placebo-treated subjects with mRS 0-3

Hi-Def

• Prospective, multi-center, double-blind, randomized, placebo-controlled clinical trial
• Total sample size = 324 ICH patients
• Study Drug
  – Active: DFO (62 mg/kg/day, up to a maximum of 6000 mg/day)
  – Placebo: Matching normal saline
  – Will be given by continuous IV infusion for 5 consecutive days
  – Will be initiated within 24h of ICH symptom onset

Hi-Def Inclusion Criteria

• Age ≥ 18 and ≤ 80 years
• NIHSS score ≥6 and GCS >6 upon presentation
• The first dose of the study drug can be administered within 24h of ICH symptom onset
• Functional independence prior to ICH, defined as pre-ICH mRS ≤1
Hemorrhagic Stroke Studies

Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH-II)
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CLEAR III

Does catheter-based intra-ventricular hemorrhage reduction alter functional outcomes in IVH survivors?

What We Thought Then and Now

1999
“Time is of the essence”
Dose = 3-10 mg
No dual cath indications
Placement away from clot
No rules to end dose

2010
Stabilizing probably makes tPA clot lysis treatment safer
Dose = 0.3 to 1 mg
Dual cath for large clots
2nd cath in clot is good
3%40, mass effect, 80%
CLEAR
Baseline Scan
(t = 0)

CLEAR III
- Sample size = 500
- 50+ sites with neurosurgical & stroke expertise
- Double-blinded, placebo-controlled, randomized trial
- Power assumption: 15% shift mRS 0-3
- ≤ 30cc ICH
- IVH obstruction of 3rd &/or 4th ventricles

Take Home
- Ischemic Stroke
  GAMES-RP, ICTuS 2/3, POINT
- Inter-cerebral Hemorrhage
  ATACH-II, HI-DEF, CLEAR III
- 12 hour window across most studies

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