Minocycline Treatment for Intra-cerebral Hemorrhage

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Introduction

- Previously submitted to NeuroNEXT Clinical Trials
- Intra-cerebral hemorrhage (ICH) very devastating type of stroke
- No effective medical treatment except for some level of BP control & surgery for large hematomas
- Volume of hematoma & associated edema are critical determinant of outcome
- Early expansion occurs in over 1/3 of patients

Matrix Metalloproteinase 9

- Matrix metalloproteinases are important mediators of BBB disruption, edema & hemorrhage
- Increased MMP-9 expression in ischemic zone
- Plasma MMP-9 increases after tPA administration
- MMPs implicated in inflammation & neural cell death

Iron

- After ICH: hemoglobin breakdown leads to high tissue levels of iron
- Iron is felt to promote ICH-induced brain edema & cell death
- Serum ferritin levels correlated with hematoma & associated edema volumes & functional outcomes
- Deferoxamine in animal models reduce edema & improve functional outcome

Minocycline

- Broad-spectrum neuro-protective agent (animal models):
  - Anti-inflammatory (reduction of leukocyte adhesion & infiltration)
  - Inhibits apoptosis
  - Direct inhibitor of MMPs
  - Iron chelator reducing neuronal injury
  - High penetration of blood brain barrier
  - Reduces infarct size in ischemic stroke model & improves functional outcome

Minocycline to Improve Neurologic Outcome in Stroke (MINOS)-2010

- Open-label, dose escalation (3, 4, 5, 6, or 10 mg/kg/day) BID for 3 days (41 received 10 mg/kg/day) given w/i 6 hours of symptoms
- 60 pts w/ ischemic strokes mean NIHSS 8.5 ± 5.8, 60% received tPA
- No hemorrhages in pts receiving tPA
- Minocycline reduced plasma MMP-9 levels especially in patients that received tPA at 24 & 72 hrs (avg. 670 ng/mL to 98 ng/mL)

Intravenous minocycline in acute stroke-2013

- 95 patients with ischemic stroke received 100 mg BID for 5 doses (started w/i 24 hrs)
- Primary outcome mRS < 3
- RR 0.94, 95% CI 0.71-1.25

Minocycline treatment in acute stroke- 2007

- Open label dosing of 200 mg PO daily for 5 days started w/i 6-24 hours in 152 pts w/ ischemic stroke
- NIHSS & mRS significantly higher in minocycline treated pts and Barthel Index higher

Efficacy of Minocycline in Acute Ischemic Stroke-2012

- Randomized single-blinded open label of minocycline 200 mg PO daily x 5 days
- NIHSS, mBI, & mRS at 1, 7, 30, & 90 days
- 50 patients
- NIHSS improved at 30 & 90 days in minocycline group
- mBI & mRS improved at 90 days
- Mortality, MI, hemorrhagic transformation, & recurrent strokes equal

MACH Pilot Trial

- Georgia Health Science University
- Pilot Phase I-II study for 24 patients started 02/13
- 400 mg total minocycline over 5 days, first dose IV
- Outcome mRS at 90 days

Minocycline Treatment in Acute Hemorrhagic Stroke for Evaluation of Treatment Efficacy and Blood Brain Barrier Permeability

- Israeli study of 150 adult patients with ICH < 24 hrs of onset
- NIHSS > 5
- Enrolling for last 2 yrs

Proposed Study

- Patients w/ ICH 18-85 yrs old that can be treated w/i 6 hours of onset of symptoms
- Double-blind, placebo-controlled RCT
- 10 mg/kg/day ÷ BID x72 hrs
- Biomarkers MMP-9, MMP-12 & ferritin @ 0, 24, & 72 hrs
- Primary outcomes: mRS & NIHSS @ 24 & 72 hours & 3 months
- Secondary outcome: ICH & edema volumes @ 24 & 72 hours, levels of biomarkers
- Safety SAEs out to 3 months

Inclusion Criteria

- Age 18-85 yrs old
- ICH volume > 1 mL
- Study drug administered w/i 6 hrs of symptom onset

Exclusion Criteria

- GCS < 6
- Planned surgical evacuation w/i 24 hours
- ICH felt to 2/2 AVM, aneurysm, trauma, or drug use
- ICH felt to 2/2 anticoagulation
- Thrombocytopenia (plt < 100k)
- Pre-existing disability (mRS > 2)

Questions

- Need Phase II study first?
- Need results of MACH & Israeli studies?
- Need to wait for ATACH study to finish?