Drug Repurposing: Development of Minocycline for Acute Ischemic Stroke

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Presenter Disclosure Information

- **David C Hess M.D.**
- **Minocycline**

FINANCIAL DISCLOSURE:

Co-Founder REACH CALL, Inc
Genentech, Boehringer Ingelheim Speaker’s Bureau

UNLABELED/UNAPPROVED USES DISCLOSURE:
Minocycline is investigational only
Dismal Record of Acute Stroke Trials
(Kidwell, Stroke 2001;32:1349)

178 controlled acute stroke trials
73,000 patients
3 “positive trials”
1 FDA-approved agent
The **One** FDA-Approved Drug (1996): Tissue Plasminogen Activator (tPA)

- 3 hour window (FDA label)
- Only 2-4% of patients with ischemic stroke receive it
- Only leads to recanalization in about 50% of patients
The No-Reflow Phenomenon
Mechanisms of tissue damage

Minocycline

- Developed as antibiotics
- Dental use (MMP inhibitors)
- Acne
"The Stroke Pipeline and Drug Development Roadmap"

<table>
<thead>
<tr>
<th>Screen</th>
<th>Optimize Lead Compound</th>
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<th>IND qualifying Phase 0</th>
<th>Phase 1</th>
<th>Phase 2</th>
<th>Phase 3</th>
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Target

Pre-clinical (STAIRS)

Minocycline

Phase III Multicenter Clinical Trials
Minocycline in focal brain ischemia

- Male SD rats 90 minute tMCA suture occlusion
- Minocycline 45 mg/kg IP bid x 2 then 22.5 mg/kg x4 doses

Yrjanheikki J et al PNAS 1999;96:13496
Anti-inflammatory effects in rodent focal ischemia model

- Minocycline reduced microglial activation

- Minocycline reduced ICE mRNA

- Minocycline reduced COX-2 and PGE2

Yrjanheikki J et al PNAS 1999;96:1346
Minocycline inhibits microglial activation, BBB damage and intracerebral hemorrhage

Yenari M, et al Stroke 2006;39:
- Male C57/BL6 mice
- TMCAo 2 hours
- MC 45 mg/kg IP 30 min and 12 h
Minocycline as effective as hypothermia
(Nagel et al, Brain Res 2008;1188:198)

Minocycline and hypothermia reduced MMP-9
Similar reduction in infarct size
Can we translate high IP doses tested in rodents to doses used in man?

Rats administered MC 90 mg/kg IP or 20 mg/kg IV

- Mean T1/2 = 2.8 hrs
- 90 mg/kg IP similar peaks to 20 mg/kg IV
- Delayed time to peak of 2.5 h with IP
- Bioavailability varied with IP: 0 to 81%
- Peritonitis in some animals with IP
Minocycline effective at “low” intravenous doses

Effects of MC on Infarct Size at 24 Hr After 90' MCAO

Xu L, et al BMC Neurology 2004
Combination of minocycline (3 mg/kg IV) with tPA

Plasma levels of MMP-9 with Mino, tPA

Minocycline and tPA Interactions

No effect of tPA’s fibrinolytic activity

Minocycline reduces ICH

Minocycline upregulates bcl-2 in neurons, but not in astrocytes and protects from OGD (Matsukawa BMC Neuroscience 2009;10:129)
Minocycline inhibits PARP-1 at nanomolar concentrations (Alano C et al PNAS 2006;103:9685)

Activity of isolated PARP 1 inhibited by DPQ, PJ-34 and minocycline
"The Stroke Pipeline and Drug Development Roadmap"

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Minocycline

Target

- PARP-1 (Alano PNAS 2006)
- Microglial MMP-9

Pre-clinical (STAIRS)

Phase III Multicenter Clinical Trials

NDA
Freezing the Penumbra

Penumbra

Penumbra at 0 hours

No Drug

"Freezing" the Penumbra

Penumbra at 0 hours

Minocycline

Penumbra at 4 hours

(Penumbra at 0 hours)

Penumbra at 4 hours

(Penumbra at 0 hours)

- Ischemic stroke
- 6-24 hrs (no tPA)
- NIH>5
  N=152

Minocycline 200 mg po
N=74
NIHSS 7.5 ±3.2

Placebo
N=77
NIHSS 7.6 ±3.8

7 days
NIHSS 6.5 ±3.8
mRS 1.5±1.4

NIHSS 8.1 ±4.4
mRS 3.1±1.3

30 days
NIHSS 1.8 ±2.1
mRS 1.1±1.2

NIHSS 7.1 ±4.4
mRS 2.7 ±1.3

90 days
NIHSS 1.6 ±1.9
mRS 0.9 ± 1.1

NIHSS 6.5 ±3.8
mRS 2.1 ± 1.2

Primary outcome: change in baseline to day 90 NIHSS

OTT 12.6 hrs

OTT 11.9 hrs

P<.0001
p<.0001
P<.0001
• NINDS-funded Phase I Study
• Dose escalation study to find MTD
• 6 hour window
• tPA allowed
• MCG/UGA, U of Kentucky, Oregon

ClinicalTrials.gov identifier NCT00630396
Objectives

1. Determine the maximally tolerated dose of IV minocycline up to 10 mg/kg in ischemic stroke patients

2. Determine the pharmacokinetics of minocycline in ischemic stroke patients

3. Gather preliminary data on functional outcomes of patients treated with minocycline

4. Determine the effect of different doses of minocycline on MMP9 activity and other inflammatory markers
<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>Overall</th>
<th>3mg/kg</th>
<th>4.5mg/kg</th>
<th>6mg/kg</th>
<th>10mg/kg</th>
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<tbody>
<tr>
<td></td>
<td>(n=80)</td>
<td>(n=11)</td>
<td>(n=4)</td>
<td>(n=4)</td>
<td>(n=41)</td>
<td></td>
</tr>
<tr>
<td>Age†</td>
<td>85.0 (13.7)</td>
<td>61.8 (10.5)</td>
<td>70.0 (11.4)</td>
<td>61.3 (9.8)</td>
<td>65.8 (15.0)</td>
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<tr>
<td>Female†</td>
<td>28 (47)</td>
<td>6 (55)</td>
<td>3 (75)</td>
<td>2 (50)</td>
<td>17 (41)</td>
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<tr>
<td>Race†</td>
<td>White</td>
<td>50 (83)</td>
<td>11 (100)</td>
<td>3 (75)</td>
<td>3 (75)</td>
<td>33 (81)</td>
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<td>Black</td>
<td>9 (15)</td>
<td>0 (0)</td>
<td>1 (25)</td>
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<td>7 (17)</td>
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<td></td>
<td>Asian</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Weight in kg†</td>
<td>81.6 (21.5)</td>
<td>89.8 (21.2)</td>
<td>69.6 (8.8)</td>
<td>68.8 (15.9)</td>
<td>81.9 (22.4)</td>
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<tr>
<td>tPA†</td>
<td>36 (60)</td>
<td>7 (64)</td>
<td>2 (50)</td>
<td>2 (50)</td>
<td>25 (61)</td>
<td></td>
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<tr>
<td>NIHSS at baseline†</td>
<td>8.7 (5.8)</td>
<td>7.2 (3.9)</td>
<td>5.5 (1.3)</td>
<td>4.3 (3.2)</td>
<td>9.8 (6.4)</td>
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<tr>
<td>Onset to Infusion Time†</td>
<td>307.4 (50.0)</td>
<td>320.4 (53.7)</td>
<td>340.5 (18.4)</td>
<td>305.8 (63.8)</td>
<td>300.8 (49.4)</td>
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</table>

† continuous variable, descriptive statistics are mean (sd)

††† categorical variable, descriptive statistics are n (%)
Minocycline

1. Safe and well tolerated up to 10 mg/kg with and without tPA

2. Ease of administration over 1 hour (field, community hospitals)

3. Long half life of 24 hours
Minocycline reduces plasma MMP-9 in tPA treated patients

Mean MMP-9 (SE) by MINO and tPA Status over Time

Mean NGAL (SE) by MINO and tPA Status over Time
Pharmacokinetics

Human subjects: Mean concentration-time curves (linear scale) for the doses studied to date: 3 (n=2); 4.5 (n=3); 6 (n=1) and 10 mg/kg (n=5). Area under the Curve (AUC) was approximately proportional over the dose range.

Rodents: Peak MC concentrations after 3 mg/kg, 10 mg/kg or 20 mg/kg IV
The issue of gender with PARP inhibitors and minocycline

- PARP inhibitors not effective in female animals in reducing ischemic damage (Hagberg H, J Neurochem 2004;90:1068; McCullough LD, JCBFM 2005;25:502)

- Minocycline a potent PARP-1 inhibitor

- Minocycline not effective in reducing infarct size in female mice (McCullough LD, JCBFM 2009 online)
Conclusions

1. Minocycline is a promising agent in ischemic stroke, especially in combination with tPA

2. Minocycline may reduce ICH associated with tPA

3. Minocycline is safe and well tolerated up to a dose of 10 mg/kg IV in humans

4. Minocycline is ready for phase IIb/III studies in combination with tPA

5. Attention will need to be given to gender issues
Phase III Clinical Trial

Large, simple trial

Combination with tPA

Time window of < 4.5 hours

But let us innovate!
Problem with our acute clinical trials in US

- Done in large academic medical centers (NINDS- 8 WELL FUNDED centers)

- Rural and community hospitals never involved. Rural patients and African Americans under-represented.

- Generalizability becomes a problem (e.g. 64% of US Hospitals did not use tPA on a Medicare patient in 2 year period)
Drip Ship RANDOMIZE

VS.

Drip RANDOMIZE Ship

VS.

Drip RANDOMIZE Keep

Stroke Patient

Community Hospital ER
(100 bed facility)

RANDOMIZE

6 hours

0

Community Hospital ER
(100 bed facility)

RANDOMIZE w/ neuroprotective agent

0

RANDOMIZE

(200 bed facility)

KEEP

PATIENT STAYS.

MONITOR ONLY

tele-consult from 3rd location

MCG
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