A Tale of Four^5 INDs
“Lessons Learned”

Richard J. Barohn, M.D.
Gertrude and Dewey Ziegler Professor of Neurology
Chair, Department of Neurology
University Distinguished Professor

University of Kansas Medical Center
Neurology/Neurosurgery Grand Rounds
January 3, 2014
“It was the best of times, it was the worst of times, it was the age of wisdom, it was the age of foolishness, it was the epoch of belief, it was the epoch of incredulity, it was the season of Light, it was the season of Darkness, it was the spring of hope, it was the winter of despair, we had everything before us, we had nothing before us.”

- Charles Dickens
A Tale of Two Cities
Investigational New Drug (IND) Application

- Provisions of the IND Regulation – 21 CFR 312
- IND is regulatory mechanism for new drug development
When an IND is needed

- A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 312.2(a)
- Submit an IND if any exempt criteria are not met
- Also certain FDA and NIH grants require an IND
When an IND **not** needed

The IND regulations \([21 \text{ CFR} \ 312.2(b)]\) state that clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements for an IND if all of the following apply:

- No change for new indication or drug labeling
- No change in advertising
- No change in route of administration, dose, patient population, or increased risks
- If approved by institutional review board and informed consent obtained
- Drug is used in an investigational study and not promoted as safe or effective and not sold commercially for which it is being studied
IND “Rules”

- You, as investigators, can read rules and decide if you are exempt
- But I recommend you write the FDA and “ask” for exempt status and ask for a written response back
- Some IRBs require such a letter from FDA
- IND application is sent to:
  Food and Drug Administration  Email Contact: Dr. Eric Bastings
  Center for Drug Evaluation and Research  russell.katz@fda.hhs.gov
  Central Document Room
  5901-B Ammendale Rd.
  Beltsville, MD  20705-1266
What are roles and responsibilities

- **Sponsor-Investigator**: an individual who both initiates and conducts an investigation, and under whose immediate direction the drug is administered or dispensed.
  - Always an individual
  - Requirements of Sponsor-Investigator include both those applicable to an investigator and a sponsor
What is involved in IND submission

- Content requirements for an IND submission are found in 21 CFR 312.23
- Essential forms for a submission:
  - 1571: must accompany every submission to the FDA for the IND
  - 1572: Statement of Investigator
  - 3674: related to clinicaltrials.gov posting
What is a 1571?

- Important: by signing you agree not to begin any clinical investigations:
  - “…until 30 days after FDA’s receipt of the IND unless I receive earlier notification by FDA that the studies may begin…”
  And;
  - “…covered by the IND if those studies are placed on clinical hold or financial hold”

- If you do not hear any response from the FDA for 30 days after the date they receive the submission, the IND is considered “in effect”.

Important: by signing you agree not to begin any clinical investigations:
What is involved in IND submission

- Essential documents for a submission:
  - Cover letter/Introductory Statement /General Investigational Plan (2-3 pages)
  - Investigator’s Brochure (if available from manufacturer; not required for single center investigator initiated trial submissions)
  - Protocol
  - Draft Informed Consent Form
  - Cross Reference Letter (provided by manufacturer which gives submission right to reference all previous data related to drug submitted to the FDA – chemistry, pharmacology and toxicology, previous human experience)
What is involved after initial IND submission?

- Continuing management of the IND is essential. Submissions to the FDA to keep them appraised of study activity includes:
  - Annual Reports (Sponsor; 312.33): due within 60 days of IND anniversary date (date the IND went into effect)
  - Unanticipated Problem Reports (Sponsor): to the FDA and any sub-sites
  - Revised Protocol (Sponsor): changes in risk/benefit of trial, change that impacts subject safety
  - Changes in the study team, study sites (Investigator)
Muscle Channelopathies

• Inherited Disorders of Muscle
• Molecular Defects in Na+, Cl-, or Ca2+ Channels
• Produce either:
  – Episodic weakness (periodic paralysis)
  – Myotonia or paramyotonia
Phase II Therapeutic Trial of Mexiletine in Non-Dystrophic Myotonia

Richard Barohn, Brian Bundy, Yunxia Wang, Laura Herbelin, Jaya Trivedi, Michael Hanna, Dipa Raja Rayan, Shannon Venance, Emma Ciafaloni, Mohammad Salajegheh, Giovanni Meola, Valeria Sansone, Alice Zanolini, Jeffrey Statland, Robert Griggs, CINCH Study Group

Supported by FDA-OPD RO1 FD 003454 & RDCRN/NIH U54 NS059065-05S1
IND #77,021
Mexiletine in NDM

Two-Period Crossover Design

Week:

1  2  3  4  | Washout Period | 6  7  8  9

N = 29 Mexiletine 200mg tid → Placebo

N = 30 Placebo → Mexiletine 200mg tid

Indicates the weeks to include for the primary endpoint analysis
Outcome Measures

- **Primary Outcome:**
  - Stiffness: self-reported using an Interactive Voice Response Diary (IVR)
    » Telephone call in daily
    » Rate stiffness, weakness, fatigue and pain on 0-9 scale

- **Secondary Outcome:**
  - Pain, Weakness, and Fatigue—IVR
  - Clinical Myotonia Assessment
  - Quality of life as measured by INQoL, SF36
  - Quantitative measure of hand grip myotonia
  - Measurement of CMAP after short and long exercise
  - Grading of Myotonia on Needle EMG
Interactive Voice Response Diary

- Primary outcome:
  - Mexiletine significantly improved stiffness on the IVR

- Secondary measures
  - Mexiletine also significantly improved pain, weakness, and tiredness on the IVR

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Treatment Effect Estimate</th>
<th>95% Confidence Interval</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVR—Stiffness</td>
<td>-2.69</td>
<td>-3.26, -2.12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IVR—Pain</td>
<td>-1.48</td>
<td>-2.03, -0.94</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IVR—Weakness</td>
<td>-1.16</td>
<td>-1.77, -0.54</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>IVR—Tiredness</td>
<td>-0.90</td>
<td>-1.49, -0.31</td>
<td>0.004</td>
</tr>
</tbody>
</table>
Mexiletine for Symptoms and Signs of Myotonia in Nondystrophic Myotonia
A Randomized Controlled Trial

Mexiletine for Treatment of Myotonia
A Trial Triumph for Rare Disease Networks
Hoffman EP, Kaminski HJ

JAMA 2012;308(13):1357-1365
Conclusion

- Mexiletine improved stiffness, pain, weakness and fatigue in NDM patients measured by IVR and quality of life measured by SF-36
  - Stiffness scores: the largest treatment mean difference
- Most frequent side effect
  - GI: 9/59 (15%) reported
- Other outcome measures currently being analyzed
- Lessons:
  - Investigator-initiated rare disease research can be done in multi-site consortium
  - Patient reported outcome measures can be primary endpoint
  - Generic drug availability can be problematic
SHORT REPORT

ABSTRACT: We initiated a randomized, double-blinded, placebo-controlled trial of intravenous immunoglobulin (IVIG) treatment in myasthenia gravis (MG). Patients received IVIG 2 gm/kg at induction and 1 gm/kg after 3 weeks vs. 5% albumin placebo. The primary efficacy measurement was the change in the quantitative MG Score (QMG) at day 42. Fifteen patients were enrolled (6 to IVIG; 9 to placebo) before the study was terminated because of insufficient IVIG inventories. At day 42, there was no significant difference in primary or secondary outcome measurements between the two groups. In a subsequent 6-week open-label study of IVIG, positive trends were observed.


RANDOMIZED, CONTROLLED TRIAL OF INTRAVENOUS IMMUNOGLOBULIN IN MYASTHENIA GRAVIS

GIL I. WOLFE, MD,1 RICHARD J. BAROHN, MD,1 BARBARA M. FOSTER, PhD,2 CARLAYNE E. JACKSON, MD,3 JOHN T. KISSEL, MD,4 JOHN W. DAY, MD, PhD,5 CHARLES A. THORNTON, MD,6 SHARON P. NATIONS, MD,1 WILSON W. BRYAN, MD,1 ANTHONY A. AMATO, MD,7 MIRIAM L. FREIMER, MD,4 GARETH J. PARRY, MD,5 and JERRY R. MENDELL, MD,4 for The Myasthenia Gravis–IVIG Study Group*

1 Department of Neurology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, Texas 75390-8897, USA
2 Academic Computing Services, University of Texas Southwestern Medical Center, Dallas, Texas, USA
3 Department of Neurology, University of Texas Health Science Center, San Antonio, Texas, USA
4 Department of Neurology, Ohio State University School of Medicine, Columbus, Ohio, USA
5 Department of Neurology, University of Minnesota School of Medicine, Minneapolis, Minnesota, USA
6 Department of Neurology, University of Rochester Medical School, Rochester, New York, USA
7 Department of Neurology, Brigham and Women’s Hospital, Harvard Medical School, Boston, Massachusetts, USA

Accepted 20 May 2002
Randomized, controlled trial of intravenous immunoglobulin in myasthenia gravis

FD-R-001352-01
IND # BB 6358

Goal: new MG and IS Dep – 2 studies

100 pts (50 each study)

IVIg 2 gm/kg & 1 gm/kg 3 wks vs. PLAC

Reality – IVIg ‘shortage’

Entered 15 pts – then study DC’d

Results: No diff in QMG (1°)

No diff in RS, SFEMG, MG-ADL (2°)

Some PLAC pts improved on SFEMG

Conc:

- Underpowered study
- Beware of placebo response
- Some things we have no control over!
- Make lemonade out of lemons
- Publish neg data
- Publish scales
# Quantitative MG Score


<table>
<thead>
<tr>
<th>TEST ITEMS</th>
<th>WEAKNESS</th>
<th>NONE</th>
<th>MILD</th>
<th>MODERATE</th>
<th>SEVERE</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade</td>
<td></td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Double vision (lateral gaze) Sec.</td>
<td>&gt;60</td>
<td>11-60</td>
<td>1-20</td>
<td></td>
<td></td>
<td>Spontaneous</td>
</tr>
<tr>
<td>Ptosis (upward gaze) Sec.</td>
<td>&gt;60</td>
<td>11-60</td>
<td>1-10</td>
<td></td>
<td></td>
<td>Spontaneous</td>
</tr>
<tr>
<td>Facial Muscles</td>
<td>Normal lid closure</td>
<td>Complete, weak, some resistance</td>
<td>Complete, without resistance</td>
<td>Incomplete</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Swallowing 4oz water (1/2 cup)</td>
<td>Normal</td>
<td>Minimal coughing or throat clearing</td>
<td>Severe coughing/choking or nasal regurgitation</td>
<td>Cannot swallow (test not attempted)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Head, lifted (45° supine) Sec.</td>
<td>&gt;120</td>
<td>&gt;30-120</td>
<td>&gt;0-30</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Right arm outstretched (90° sitting) Sec.</td>
<td>&gt;240</td>
<td>&gt;90-240</td>
<td>&gt;10-90</td>
<td></td>
<td></td>
<td>0-10</td>
</tr>
<tr>
<td>Left arm outstretched (90° sitting) Sec.</td>
<td>&gt;240</td>
<td>&gt;90-240</td>
<td>&gt;10-90</td>
<td></td>
<td></td>
<td>0-10</td>
</tr>
<tr>
<td>Speech following counting aloud from 1-50 (onset of dysarthria)</td>
<td>None at #50</td>
<td>Dysarthria at #30-49</td>
<td>Dysarthria at #10-29</td>
<td>Dysarthria at #9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Right leg outstretched (45° supine) Sec.</td>
<td>&gt;100</td>
<td>31-100</td>
<td>1-30</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Left leg outstretched (45° supine) Sec.</td>
<td>&gt;100</td>
<td>31-100</td>
<td>1-30</td>
<td></td>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Vital capacity (1): male female</td>
<td>&gt;3.5</td>
<td>&gt;2.5-3.5</td>
<td>&gt;1.5-2.5</td>
<td>&lt;1.5</td>
<td>&lt;1.5</td>
<td></td>
</tr>
<tr>
<td>Rt hand grip (KgW): male Female</td>
<td>&gt;45</td>
<td>&gt;15-45</td>
<td>5-15</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td></td>
</tr>
<tr>
<td>Left hand grip (KgW): male Female</td>
<td>&gt;35</td>
<td>&gt;15-35</td>
<td>5-15</td>
<td>&lt;5</td>
<td>&lt;5</td>
<td></td>
</tr>
</tbody>
</table>

Total QMG Score: ___________________________
## MG Activities of Daily Living (ADL) Scale

<table>
<thead>
<tr>
<th>GRADE</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>SCORE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Talking</td>
<td>Normal</td>
<td>Intermittent slurring or nasal speech</td>
<td>Constant slurring or nasal, but can be understood</td>
<td>Difficult to understand speech</td>
<td></td>
</tr>
<tr>
<td>Chewing</td>
<td>Normal</td>
<td>Fatigue with solid food</td>
<td>Fatigue with soft food</td>
<td>Gastric tube</td>
<td></td>
</tr>
<tr>
<td>Swallowing</td>
<td>Normal</td>
<td>Rare episode of choking</td>
<td>Frequent choking necessitating changes in diet</td>
<td>Gastric tube</td>
<td></td>
</tr>
<tr>
<td>Breathing</td>
<td>Normal</td>
<td>Shortness of breath with exertion</td>
<td>Shortness of breath at rest</td>
<td>Ventilator dependence</td>
<td></td>
</tr>
<tr>
<td>Impairment of</td>
<td>None</td>
<td>Extra effort, but no rest periods needed</td>
<td>Rest periods needed</td>
<td>Cannot do one of these functions</td>
<td></td>
</tr>
<tr>
<td>ability to brush</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>teeth or comb hair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Impairment of</td>
<td>None</td>
<td>Mild, sometimes uses arms</td>
<td>Moderate, always uses arms</td>
<td>Severe, require assistance</td>
<td></td>
</tr>
<tr>
<td>ability to arise</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>from a chair</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Double vision</td>
<td>None</td>
<td>Occurs, but not daily</td>
<td>Daily, but not constant</td>
<td>Constant</td>
<td></td>
</tr>
<tr>
<td>Eye droop</td>
<td>None</td>
<td>Occurs, but not daily</td>
<td>Daily, but not constant</td>
<td>Constant</td>
<td></td>
</tr>
</tbody>
</table>

**TOTAL MG ADL SCORE**
Papers from MG-IVIG Negative Trial

Phase II Trial of Methotrexate in Myasthenia Gravis
FDA OPD - RO1 FD003538
IND #101,306

Richard J. Barohn, MD, Mamatha Pasnoor, MD
Laura Herbelin, BSc, Mazen Dimachkie, MD
Jianghua He, PhD
& the MG Methotrexate Muscle Study Group
Study Design

- Randomized, double-blind, placebo-controlled study
- To determine if oral methotrexate is a safe and effective therapy for myasthenia gravis (MG) patients who are on prednisone
IND 101,306

Richard Barohn, MD
3901 Rainbow Blvd., Mail Stop 2012
Kansas City, KS 66160

Dear Dr. Barohn:


After reviewing the information contained in your submission, we have concluded that your study meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA will not accept your application.
Phase II Trial of Methotrexate in MG
Barohn and Muscle Study Group
FDA OPD R01 FD003538/IND #101,306

- A randomized, double-blind, placebo-controlled study
- 50 patients
  - 25 receiving MTX/25 receiving placebo/12 mo study
- Specific aim – determine if oral MTX is an effective therapy for MG patients who are on prednisone
- Hypothesis – adding MTX therapy will improve the MG manifestations so that prednisone dose can be reduced and clinical measures of MG severity will improve
- The primary measure of efficacy will be the 9-month prednisone area under the curve (AUC)
- Secondary: QMG, MG ADL, MG Comp, MG QOL15
Polyglutamation Assay – with Children’s Mercy Hospital
Mara Becker, MD (PI) and Steve Leeder, PharmD, PhD

- MTX bioactivated to the polyglutamated form of methotrexate (MTXgluₙ) by folylpolyglutamyl synthase (FPGS)
- Polyglutamation determines the biologic activity of methotrexate
- Amount of polyglutamation is variable from patient to patient
- Rheumatoid arthritis lit suggests patients with highly polyglutamated methotrexate respond better
- Additional blood draw at month 12
- Personalized medicine approach
Status of enrollment

- 58 subjects screened
- 51 subjects enrolled, 6 screen failures:
  - ALT (2), too strong (2), 1 decided against, 1 thymoma
- 5 drop-out:
  - 1 for Parkinson new diagnosis
  - 1 for ALT elevation
  - 1 myalgia
  - 1 personal (travel)
  - 1 did not feel well
- Last subject finished late 2013
- Final data analysis in progress
ANNALS OF THE NEW YORK ACADEMY OF SCIENCES

Issue: Myasthenia Gravis and Related Disorders

Phase II trial of methotrexate in myasthenia gravis

Mamatha Pasnoor, Jianghua He, Laura Herbelin, Mazen Dimachkie, Richard J. Barohn, and the Muscle Study Group

University of Kansas Medical Center, Kansas City, Kansas
Rituximab For Myasthenia Gravis

- PI – R. Nowack
- CoPIs – J. Goldstein, M. Dimachkie, R. Barohn
- Just Funded by NeuroNext/NIH
- ACH R – Ab positive
- 50 pts; 2:1 randomization
- IND Exempt!
IND 116878

ACKNOWLEDGE/EXEMPT IND

Jonathan M. Goldstein, MD
Department of Neurology
Yale University School of Medicine
800 Howard Avenue, Lower Level
New Haven, CT 06510

Dear Dr. Goldstein:

We acknowledge receipt of your Investigational New Drug Application (IND), submitted October 29, 2012, received October 31, 2012, under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Rituxan (rituximab) injection.

After reviewing the information contained in your submission, we have concluded that your study meets all of the requirements for exemption from the IND regulations and, therefore, an IND is not required to conduct your investigation. In accordance with 21 CFR 312.2(b)(4) of the regulations, FDA will not accept your application.
Phase II Studies of Rasagiline in Amyotrophic Lateral Sclerosis:
36 patient open-label screening study
No IND #
80 patient placebo-controlled study
IND #104,360
FDA OPD - RO1 FD003739

Principal Investigators:
Richard J. Barohn, MD
Yunxia Wang, MD
Jon Katz, MD
Russell Swerdlow, MD
and the WALS and MSG
Why Rasagiline

- Rasagiline has broad neuroprotective activity in neuronal cell culture system that may occur at a mitochondrial level
- Mitochondrial dysfunction occurs in ALS patients
- Another drug that is closely related to a compound that is effective in Parkinson’s disease, R-pramipexole, is believed to modulate at mitochondrial level, but Phase 3 ALS results are negative
- Rasagiline prolongs survival in the SOD1 mouse model of ALS
- Small Israeli ALS clinic experience (Drory)
- European study starting - Ludolph
Rasagiline-Open Label Study Design

- Phase II, open label; 2 mg/day for 12 months
- No IND #: exempt
- TEVA investigator initiated grant – PI: Yunxia Wang, MD, University of Kansas Medical Center
- Sites: Western ALS Study Group (WALS)
  - University of Kansas Medical Center
  - University of Nebraska
  - McGill University
  - California Pacific Medical Center
  - University of Pennsylvania
  - Phoenix Neurological Institute
  - University of Iowa
  - University of Minnesota
  - The Methodist Hospital System
ALSFRS-R

1. Speech
   4 – Normal
   3 – Detectable speech with disturbances
   2 – Intelligible with repeating
   1 – Speech combined with nonvocal communication
   0 – Loss of useful speech

2. Salivation
   4 – Normal
   3 – Slight but definite excess of saliva in mouth; may have nighttime drooling
   2 – Moderately excessive saliva; may have minimal drooling
   1 – Marked excess of saliva with some drooling
   0 – Marked drooling; requires constant tissue or handkerchief

3. Swallowing
   4- Normal
   3- Early eating problems – occasional choking
   2- Dietary consistency changes
   1- Needs supplemental tube feeding
   0- NPO (exclusively parenteral or enteral feeding)

4. Handwriting
   4- Normal
   3- Slow or sloppy; all words are legible
   2- Not all words are legible
   1- able to grip pen but unable to write
   0- Unable to grip pen

5. 5a. Cutting Food and Handling Utensils (patients without gastrostomy)

5b. Cutting Food and Handling Utensils (alternate scale for patients with gastrostomy)

6. Dressing and Hygiene

7. Turning in bed and adjusting bed clothes

8. Walking

9. Climbing Stairs

10. Dyspnea

11. Orthopnea

12. Respiratory Insufficiency

Maximum score: 48
Rasagiline – Open Label Study Design

- **Aims:**
  - Determine whether rasagiline is safe in this patient population and if the drug has the potential to slow ALS disease progression
  - Determine if mitochondrial function biomarkers are affected by rasagiline prior and after the rasagiline treatment

- **Use of WALS Historical Controls**
Six Month ALSFRS-R Rasagiline versus Historical Control

### Slope Deterioration of ALSFRS-R per Month

<table>
<thead>
<tr>
<th></th>
<th>Rasagiline Treatment at 6 Months</th>
<th>Historical Controls at 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 31</td>
<td>0.96/month (95% CI -0.19 - 0.44)</td>
<td>1.08/month (95% CI 0.99-1.17)</td>
</tr>
</tbody>
</table>

p-value = 0.44

* Western ALS Study Group 1997-2007; Baseline FVC >75%, Symptom duration < 3 years for Treatment & Control Groups
Twelve Month ALSFRS-R Rasagiline versus Historical Control

<table>
<thead>
<tr>
<th>Number Treated</th>
<th>N=36</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>Male: 18 (50%) Female: 18 (50%)</td>
</tr>
<tr>
<td>Mean Age (years)</td>
<td>60.8</td>
</tr>
<tr>
<td>Mean Baseline ALSFRS-R</td>
<td>38.45</td>
</tr>
<tr>
<td>Mean Baseline Vital Capacity %</td>
<td>99.9</td>
</tr>
<tr>
<td>Mean Baseline Weight (lbs)</td>
<td>177</td>
</tr>
</tbody>
</table>

Rasagiline ALSFRS-R slope = 1.18/month
Mitochondrial Biomarker Assays

- Mito membrane potential on lymphocyte mitos
  - JC1 ratio flow cytometry
  - Lymphocyte mitotracker flow cytometry
- Apoptosis markers in lymphocytes
  - Phosphatidylserine-annexin assay
- Oxidative stress markers in blood
  - Oxygen Radical Antioxidant Capacity (ORAC) assay
- Bcl2/Bax ratios on blood protein lysates
  - Rationale: Bcl2/Bax RNA ratio changes in cell culture
Serum Biomarkers: Mito Membrane Potentials

Both evaluate mitochondria polarization. An increase in the ratio indicates hyperpolarization which is thought to be protective for cells by preventing cell death. After 12 months of treatment, mitochondria were relatively hyperpolarized.
Evaluates the display of specific proteins on mitochondria that occurs when a cell is undergoing apoptosis.
Bcl2/Bax Ratio

Bcl is thought to be anti-apoptotic and Bax is pro-apoptotic. When we see an increase in this ration (Bcl/Bax), it indicates the cell is moving away from apoptosis and is being protected from cell death.
Oxygen Radical Antioxidant Capacity (ORAC) Assay

Measures the antioxidant effect on cells and protection from damaging free radicals. Another protective mechanism of rasagiline
Possible mitochondrial target engagement in an open label trial of rasagiline for ALS


Poster #P311, International Symposium on ALS/MND, Milan, Italy.

*Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2013;14(Suppl 2):230.*
Conclusion

- There is scientific rational to study rasagiline in ALS
- Rasagiline is safe in this population
- We may be demonstrating mitochondrial target engagement
- We may be demonstrating a biomarker measure of disease progression
- CTSA Ethics Consultation –
  - OK to proceed if pts informed of Ras 36 benefits
- Next steps:
  - Publish data
  - Begin 80 patient placebo controlled study
Rasagiline 80 – Randomized Placebo Controlled Trial

- IND# 104,360
- Funded by FDAOPD RO1-003739, September 2012
- PI is Richard J. Barohn; Co-PI’s: Yunxia Wang, Russell Swerdlow (KUMC), Jonathan Katz (CPMC)
  - 12 month placebo-controlled study
  - 3:1 randomization (60 on rasagiline 2 mg/day, 20 on placebo)
    - Using WALS Historical Controls bleed-in
- Biomarkers
  - Swerdlow mito markers
  - Urine oxid stress marks (Columbia)
    - Isoprostane levels
    - Urinary 8-oxodG levels
  - Brain Glutathione MRS
  - TDP 43 in platelets
Phase II Study of Arimoclomol in IBM

FDA-IND # 76,773

PI: Mazen M. Dimachkie
Co-PI: Michael Hanna
Co-I: Richard J. Barohn
Pedro Machado
Linda Greensmith
<table>
<thead>
<tr>
<th>Age of Onset</th>
<th>Rash</th>
<th>Pattern of Weakness</th>
<th>CK</th>
<th>Muscle Biopsy</th>
<th>Cellular Infiltrate</th>
<th>Response to Therapy</th>
<th>Commonly Associated Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elderly</td>
<td>No</td>
<td>Asymmetry Finger flexor,</td>
<td>NL or up to 10xNL</td>
<td>Rimmed vacuoles; endomysial inflammation with invasion</td>
<td>CD8+T-cells; macrophage &amp; Myeloid Dendritic Cells</td>
<td>No</td>
<td>Autoimmune disorder: SS, SLE, thrombocytopenia &amp; sarcoidosis</td>
</tr>
<tr>
<td>(most of IIM &gt;50)</td>
<td></td>
<td>knee extensor, dysphagia</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Arimoclomol

- Derivative of Bimoclomol, developed by CytRx, a potent co-inducer of Heat Shock Proteins
- Stabilizes Heat Shock Transcription Factor-1 (HSF-1)
  - This increases levels of HSP70 and HSP90
- Interacts with acidic membrane lipids to stabilize plasma membranes
- Interacts with cardiolipin in mitochondria
  - May stabilize membrane
  - May inhibit apoptosis
- May slow down the process of protein misfolding and aggregation in IBM

Arimoclomol at dosages up to 300 mg/day is well tolerated and safe in amyotrophic lateral sclerosis.
Arimoclomol Mechanism

**Normal Cell**
- DNA → RNA
- Blueprint to make protein → Normal protein

**Diseased Cell**
- DNA → RNA
- Mutation
- DNA → RNA
- Chaperone
- Decision
- Tagged for Degradation
- Degraded protein
- Repair → Normal protein

Arimoclomol amplifies cell signal to make molecular “chaperone”

Normal protein → Chaperone Complex → Decision

Tagged for Degradation

Degraded protein

Repair → Normal protein

Normal protein
Design

- Randomised double blind placebo controlled study (2:1)
- Funded through GCRC Junior Investigator Grant and MRC
- Kansas, USA: 12 patients
- London, UK: 12 patients
- Treatment phase: 4 months
- Follow-up phase: 8 months
- Treatment = Arimoclomol 100 mg PO TID: 4 months (Mandated by FDA)
- Follow for 12 months for clinical measurements
Outcome Measures

- Primary is safety and tolerability:
  - Adverse event reporting
  - Labs
- Secondary
  - Muscle strength testing:
    » QMA/MVICT 6 muscles bilaterally
    » MMT
  - IBMFRS
  - DEXA fat-free mass
  - Muscle biopsy – HSP 70 levels/histology
1. **SWALLOWING**
   - 4 Normal
   - 3 Early eating problems – occasional choking
   - 2 Dietary consistency changes
   - 1 Frequent choking
   - 0 Needs tube feeding

2. **HANDWRITING** *(with dominant hand prior to IBM onset)*
   - 4 Normal
   - 3 Slow or sloppy; all words are legible
   - 2 Not all words are legible
   - 1 Able to grip pen but unable to write
   - 0 Unable to grip pen

3. **CUTTING FOOD AND HANDLING UTENSILS**
   - 4 Normal
   - 3 Somewhat slow and clumsy, but no help needed
   - 2 Can cut most foods, although clumsy and slow; some help needed
   - 1 Food must be cut by someone but can still feed slowly
   - 0 Needs to be fed

4. **FINE MOTOR TASKS** *(opening doors, using keys, picking up small objects)*
   - 4 Independent
   - 3 Slow or clumsy in completing task
   - 2 Independent but requires modified techniques or assistive devices
   - 1 Frequently requires assistance from caregiver
   - 0 Unable

5. **DRESSING**
   - 4 Normal
   - 3 Independent but with increased effort or decreased efficiency
   - 2 Independent but requires assistive devices or modified techniques (Velcro snaps, shirts without buttons, etc.)
   - 1 Requires assistance from caregiver for some clothing items
   - 0 Total dependence

6. **HYGIENE** *(Bathing and toileting)*
   - 4 Normal
   - 3 Independent but with increased effort or decreased activity
   - 2 Independent but requires use of assistive devices (shower chair, raised toilet seat, etc.)
   - 1 Requires occasional assistance from caregiver
   - 0 Completely dependent

7. **TURNING IN BED & ADJUSTING COVERS**
   - 4 Normal
   - 3 Somewhat slow & clumsy but no help needed
   - 2 Can turn alone or adjust sheets but with great difficulty
   - 1 Can initiate but not turn or adjust sheets alone

8. **SIT TO STAND**
   - 4 Independent (without use of arms)
   - 3 Performs with substitute motions (leaning forward, rocking) but without use of arms
   - 2 Requires use of arms
   - 1 Requires assistance from device/person
   - 0 Unable to stand

9. **WALKING**
   - 4 Normal
   - 3 Slow or mild unsteadiness
   - 2 Intermittent use of assistive device (AFO, cane, walker)
   - 1 Dependent on assistive device
   - 0 Wheelchair dependent

10. **CLIMBING STAIRS**
    - 4 normal
    - 3 Slow with hesitation or increased effort; uses handrail intermittently
    - 2 Dependent on handrail
    - 1 Dependent on handrail and additional support (cane or person)
    - 0 Cannot climb stairs
Results: Adverse Events

- 8 treatment-related adverse events in PBO
- 14 treatment-related adverse events in arimoclomol
  - Constipation (3)
  - hyponatremia (2), loose stools (2)
  - 1 in each: GI problems, gas pains, nausea, cramps, dizziness/tinnitus, hypertension & RA
- Most common gastrointestinal
- One Serious Adverse Event but none of the adverse events led to drug discontinuation.
Results:
IBMFRS

![Bar chart showing change in IBMFRS sum score for 4M, 8M, and 12M periods with significance levels for comparison between Arimoclomol and Placebo groups.]

- 4M (n=16 vs 8):
  - Arimoclomol: -0.34
  - Placebo: -0.88
  - p = 0.239

- 8M (n=14 vs 8):
  - Arimoclomol: -0.68
  - Placebo: -2.50
  - p = 0.055

- 12M (n=15 vs 8):
  - Arimoclomol: -2.03
  - Placebo: -3.50
  - p = 0.538
## Pilot Study of Arimoclomol in IBM: Efficacy

<table>
<thead>
<tr>
<th>Outcome Variable</th>
<th>Arimoclomol change</th>
<th>Placebo change</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IBMFRS score, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4M (n=16+8)</td>
<td>-0.34±1.38</td>
<td>-0.88±1.157</td>
<td>0.239</td>
</tr>
<tr>
<td>8M (n=14+8)</td>
<td>-0.68±1.58</td>
<td>-2.50±3.31</td>
<td>0.055</td>
</tr>
<tr>
<td>12M (n=15+8)</td>
<td>-2.03±2.68</td>
<td>-3.50±3.35</td>
<td>0.538</td>
</tr>
<tr>
<td>Average MMT score, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4M (n=15+8)</td>
<td>-0.04±0.19</td>
<td>-0.12±0.20</td>
<td>0.561</td>
</tr>
<tr>
<td>8M (n=13+8)</td>
<td>-0.12±0.22</td>
<td>-0.26±0.27</td>
<td>0.147</td>
</tr>
<tr>
<td>12M (n=14+7)</td>
<td>-0.21±0.21</td>
<td>-0.35±0.20</td>
<td>0.232</td>
</tr>
<tr>
<td>MVICT sum score, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4M (n=14+8)</td>
<td>0.46±12.11</td>
<td>-0.30±14.49</td>
<td>0.633</td>
</tr>
<tr>
<td>8M (n=13+8)</td>
<td>7.20±19.65</td>
<td>-1.71±17.80</td>
<td>0.347</td>
</tr>
<tr>
<td>12M (n=14+8)</td>
<td>-1.21±20.76</td>
<td>0.52±17.98</td>
<td>0.946</td>
</tr>
<tr>
<td>DEXA body fat free mass percentage, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4M (n=15+8)</td>
<td>1.3±1.3</td>
<td>1.9±2.8</td>
<td>0.949</td>
</tr>
<tr>
<td>12M (n=14+8)</td>
<td>-2.0±3.8</td>
<td>-1.0±2.0</td>
<td>0.339</td>
</tr>
<tr>
<td>HSP70 levels (ng/100ng myosin), mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4M (n=15+8)</td>
<td>-110.72±757.40</td>
<td>-34.70±336.35</td>
<td>0.466</td>
</tr>
</tbody>
</table>
Arimoclomol for IBM: Conclusions

- Arimoclomol showed good safety & tolerability
- Trend towards a slower deterioration observed in the arimoclomol group
- No change in HSP-70 levels
- Arimoclomol is well tolerated in IBM & may be effective
- Supports further research of arimoclomol in IBM
- Submitted to NeuroNEXT – rejected
- Submitted to FDA-OPD for 150 pt study
- FDA OPD R01 under review (M. Dimachkie, PI)
Conclusions

- Investigator initiated research in neuromuscular disease is viable
  - Novel drugs
  - Re-purposed drugs
  - Imp component of discovery journey
- Involves multiple team members/multiple sites
- Get involved early: med students, residents, fellows
- Some but not all drug trials require an IND
  - IND rules are complex
    - Check with your local regulatory team sponsors
- Clinical endpoint scales important
- Biomarker endpoints may be even more important, esp in an otherwise negative or underpowered study and lead to future research
- If either clinical or biomarkers are positive in early phase – considered doing next study
- Write! Write! Write!
- It maybe the worst of times, but also the BEST of times.