The Paradox of Phase II ALS Trials

A Statistical Conundrum

James D. Berry, MD, MPH
MGH Neurological Clinical Trials Institute
November 19, 2014
Why have so many Late Stage ALS trials “failed?”

• ALS is a complex disease, with multiple potential targets for modification.
• Phase II trials will never predict the results of Phase III studies perfectly.
• The key paradox of Phase II trials:
  – We want efficacy data
  – With few participants
  – And short trial durations
  – Using the same outcome measures as Phase III trials.
• Biomarkers might minimize the paradox by showing
  1. Drug levels (pharmacokinetics)
  2. Target engagement (pharmacodynamics)
  3. Changes in biochemical pathways related to target engagement
  4. Efficacy
Amyotrophic Lateral Sclerosis (ALS)

- Motor Neuron Disease affecting upper and lower motor neurons.
- Classic Tagline: “Progressive painless weakness.”
- Asymmetric onset, regional spread
- Average time from symptom onset to diagnosis is 12-14 months
  - Longer time = improved prognosis
- Average survival after symptom onset is 3-5 years
  - Wide variability
- Spares EOM and bowel/bladder until very late in disease (pts on ventilators)
- May be a group of pathophysiologically and/or genetically distinct diseases manifesting in similar clinical symptoms.
- No known cure.
- One FDA-approved medication is riluzole.
- Active area of genetic, pathological, and clinical research.

Theories of ALS Pathophysiology

- RNA Translation Dysregulation
- Mitochondrial Dysfunction
- Oxidative Damage
- Inflammation-mediated damage
- Glutamate Excitotoxicity
- Axonal Transport Breakdown (Protein Aggregation)
- Loss of Neuromuscular Junction Viability
- Motor Neuron
Challenges in ALS Clinical Trials

- **ALS is Rare, Degenerative, and Fatal**
  - Affects enrollment and follow-up

- **No Prodrome**
  - When does disease begin?

- **Unclear Pathophysiology**
  - Appropriate drug targets?

- **Limited Preclinical Models**
  - Which candidate drugs move forward?

- **High Disease Variability**
  - What outcome measure is best?

- **Lack of Biomarkers**
  - How do we identify patients early, follow intermediate outcomes, and unravel pathophysiology?

- **Trials**
  - Size, Duration, Cost
  - Patient immobility
  - Placebo Burden

- **NOT Unique to ALS**
Traditional Outcome Measures

1. Tracheostomy-Free Survival
2. Vital Capacity
3. Hand-Held Dynamometry
4. Revised ALS Functional Rating Scale
   - 48 point, 12 question scale that records functional ability of patient in numerous realms
     • Arms, legs, bulbar, respiratory
   - Validated for use in person or over a phone, and for a caregiver to answer on behalf of a patient
   - Variability is remarkably low for a subjective scale, but trial size could be reduced by an outcome measure with a lower variability.

   • **Sample Size for ALSFRS-R**
     *(90% power, p-value 5%, 1 year, 2 arms)*
     - 30% slowing of disease (1.0 pt/mo → 0.7 pt/mo) 356 patients
     - 40% slowing of disease (1.0 pt/mo → 0.6 pt/mo) 200 patients
Outcome Measure Challenges

• **Survival** –
  – low event rate over a relatively short trial;
  – complicated by people who elect to have tracheostomy;
  – therapy may affect function/QoL without affecting survival.

• **VC** –
  – limited scope/only gives readout on one population of motor neurons;
  – disease can affect respiration at very different times and rates (variability);
  – bulbar weakness affects outcome
Outcome Measure Challenges

• **HHD** –
  – difficult to summate (either too limited or too broad in scope);
  – not truly quantitative;
  – variability is no better than other outcomes;
  – ceiling and floor effects

• **ALSFRS-R** –
  – may give too broad a picture;
  – variability;
  – subjective rating;
  – can improve with treatment;
  – Racsh analyses mixed;
  – defining clinically “meaningful change” is an issue;
  – does not progress to 0 – analysis complicated by death
CAFS: Combined Assessment of Function and Survival

1. Determine functional change or time of death for each patient

   - Subject A: 15 point decrease

   - ALSFRS-R:
     - Day 0
     - Trial end
     - 15 point functional decrease from baseline

2. Compare patient's outcome to each other patient in trial

   - All Other Subjects:
     - Subject A: -5
     - Subject B: -10
     - Subject C: -20
     - Died in 10 months
     - Died in 1 month

3. Score patients based on relative function or time of death

   - If...
     - Better function or died later than comparison: +1
     - Same function or died at the same time as comparison: 0
     - Worse function or died before comparison subject: -1

   - Score:
     - Subject A:
       - 15 point functional decrease
       - Score: +1
       - Died in 10 months
     - Summated Score: +1

     - Subject B:
       - 5 point functional decrease
       - Score: +1
       - Died in 10 months
     - Summated Score: +5
The end result is a non-parametric group comparison that compares functional decline while accounting for deaths and missing data for the ALSFRS-R.
Newer Outcome Measures

• Accurate Test of Limb Isometric Strength (ATLIS)
  – Quantitative strength testing
• Electrical Impedence Myography (EIM)
  – Non-invasive electrodiagnostic technique; still in validation
• Motor Unit Number Estimation
  – Time consuming, little statistical advantage over current outcomes
• PET (inflammatory ligands)?
• Biofluid Biomarkers – pNFH, NFL, urate?

BUT IN REALITY

• These only add something if they add statistical advantage*
  – This is the hardest thing to know about these markers

* PET and Biofluid markers may also add biological insight
• Neuralstem cells engrafted into the spinal cord (Phase II; no placebo)

• NurOwn ™ Adult bone marrow-derived Mesenchymal Stromal Cells (Phase II; + placebo)

• What if sham surgery worsens people and treatment rescues that worsening?
Prediction models

• Using PRO-ACT
  – based on 3 months progression
  – predict 12 months of progression

• Estimates suggest 20% power improvement over standard models using models to guide study enrollment
  – Presumably do not exclude more patients, just exclude more appropriately
  – Requires a lead-in phase
Questions

• Using historical controls from PRO-ACT?
• Futility design trials?
• Use prediction models to compare expected to observed disease progression – how good is good enough?
• Include observational arm for invasive studies?
• Require markers of target engagement for new trials?
Acknowledgements

PALS and their Caregivers and Loved Ones

Neurologists
Merit Cudkowicz
Bill David
Steve Han
Nazem Atassi
Elena Ratti
Sabrina Paganoni

Fellows
Harry Banno
Katherine Nicholson

NP
Darlene Sawicki

PTs
Pat Andres
Amy Swartz

ST
Paige Nalipinski

RT
Dean Hess

Coordinators
Alyssa Murphy
Julia Yasek
Fernando Gonterman
Jenna Wells
Courtney Ortiz
Kellen Haley
Mark Levine-Weinberg

Nurses
Jen Scalia
Melissa Arnold
Sarah Cornacchio
Katie Tee