Current Clinical Trials in ALS

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1. Clinical trials in ALS: Past & Present
2. Upcoming trials
3. How to prepare
1. ALS Clinical Trials: Past & Present

• THE GOOD:
  – Motivated patients
  – Experienced site staff
2. ALS Clinical Trials: Past & Present

• THE GOOD:
  – Motivated patients
  – Experienced site staff

• THE BAD:
  – Comparing McIntosh to Granny Smith Apples
  – Limited resources
  – Trial design
In BENEFIT-ALS, 711 patients with amyotrophic lateral sclerosis (ALS) were enrolled into the open-label phase; subsequently 605 patients were randomized 1:1 to double-blind treatment with either tirasemtiv or placebo for 12 weeks. As previously announced, BENEFIT-ALS did not achieve its primary efficacy endpoint, the mean change from baseline in the ALS Functional Rating Scale in its revised form (ALSFRS-R). Secondary endpoints evaluated measures of respiratory performance and other measures of skeletal muscle function and fatigability.

Treatment with tirasemtiv resulted in a statistically significant and potentially clinically meaningful reduction in the decline of Slow Vital Capacity (SVC, a measure of the strength of the skeletal muscles responsible for breathing) that has been shown to be an important predictor of disease progression and survival in prior trials of patients with ALS. This pre-specified secondary efficacy endpoint also declined less on tirasemtiv than on placebo at each assessment time point.

<table>
<thead>
<tr>
<th>Slow Vital Capacity</th>
<th>Placebo (n = 210)</th>
<th>Tirasemtiv (n = 178)</th>
<th>All (N = 388)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (% Predicted, mean ± SD)</td>
<td>89.7 (17.2)</td>
<td>85.7 (19.3)</td>
<td>87.8 (18.3)</td>
</tr>
<tr>
<td>Time Point</td>
<td>Changes from Baseline (Least Square Mean ± Standard Error)</td>
<td>p-value</td>
<td></td>
</tr>
<tr>
<td>Week 4</td>
<td>-3.89 (0.62)</td>
<td>-0.99 (0.68)</td>
<td>0.001</td>
</tr>
<tr>
<td>Week 8</td>
<td>-5.81 (0.68)</td>
<td>-2.85 (0.77)</td>
<td>0.004</td>
</tr>
<tr>
<td>Week 12</td>
<td>-8.66 (0.80)</td>
<td>-3.12 (0.90)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Slope of decline (Percentage Points per day)</td>
<td>0.0905</td>
<td>0.0394</td>
<td>0.0006</td>
</tr>
</tbody>
</table>
2. ALS Clinical Trials: Past & Present

• THE GOOD:
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• THE UGLY:
  – Only 1 positive trial
ALS Clinical Trial Targets

Auto Immunity
- Cyclophosphamide
- Plasmapheresis
- IVlg
- Total Lymphoid Irradiation
- Cyclosporine

Excitotoxicity
- Dextromethorphan
- Gabapentin
- Lamotrigine
- Topiramate
- Talampanel
- Riluzole

Neurotrophic Factors
- GH
- IGF-1
- CNTF
- BDNF
- GDNF
- Xaliproden

Glutamate Transporter
- Beta-Lactam Antibiotics

Mitochondria
- Creatine
- CoEnzyme Q10

Apoptosis
- Pentoxifylline
- TCH-346
- Valproic Acid
- Lithium

Strength
- Guanidine
- Physostigmine
- 3,4-Diaminopyridine
- Theophylline
- Tirasemtiv

Anti Oxidants
- N-Acetyl Cysteine

Innate Immunity
- Celecoxib
- Minocycline
- Glatiramer Acetate
- Pioglitazone
- NP001

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ABSTRACT: Amyotrophic lateral sclerosis (ALS) is proving intractable. Difficulties in pre-clinical studies contribute in small measure to this futility, but the chief reason for failure is an inadequate understanding of disease pathogenesis. Many acquired and inherited processes have been advanced as potential causes of ALS but, while they may predispose to disease, it seems increasingly likely that none leads directly to ALS. Rather, two recent overlapping considerations, both involving aberrant protein homeostasis, may provide a better explanation for a common disease phenotype and a common terminal pathogenesis. If so, therapeutic approaches will need to be altered and carefully nuanced, since protein homeostasis is essential and highly conserved. Nonetheless, these considerations provide new optimism in a difficult disease which has hitherto defied treatment.
Building Better Trials

- Lack of biomarkers
- Heterogeneous patient population
- Phase II Trial Paradox
  → Endpoints
Joint-rank Scoring: Theoretical Trial

- At the end of the trial, functional decline OR survival time is determined for each patient.
- All patients are ranked on the same scale, from best to worst outcome, and given a rank number.
- Unblinding occurs after the ranks have been assigned; means of rank in each group are compared.

<table>
<thead>
<tr>
<th>Joint Rank</th>
<th>Functional Decline at Trial End</th>
<th>Survival Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>ALSFRS-R (change)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>-12% &gt; -25% &gt; -30% &gt; -33% &gt; -41%</td>
<td>3  10.5 months</td>
</tr>
<tr>
<td>6</td>
<td></td>
<td>2  3.3 month</td>
</tr>
<tr>
<td>5</td>
<td></td>
<td>1  1 month</td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Patients who survived (ordered by functional decline)

Patients who died (ordered by survival time)

2. Upcoming Trials

- Biogen-ISIS SOD1+ & C9orf72+
- *Withania somnifera* (NIALS)
- Cytokinetics Phase 3 *tirasemtiv*
- Neuraltus Phase 3
- Stem cells
- GSK *ozanezumab* Phase 3?
Non-treatment projects

• Canadian Neuromuscular Disease Registry (www.cndr.org)

• CALS Neuroimaging consortium MRI study

• Brain Bank
Translational Research

Research Grants

Arthur J. Hudson Translational Team Grant

The 2014 vision of ALS Canada is “Within ten years, ALS will be a treatable disease.” To that end, ALS Canada’s Strategic Plan for Research (2014-2017) established the goal to develop, through a national network, at least one novel therapeutic strategy to slow the progression of ALS. As a mechanism to achieve that goal, the Arthur J. Hudson Translational Team Grant has been established.
3. How to prepare?

- Montreal Neurological Institute as a **key site**
  - Infrastructure of the CRU
  - Research background
  - Dr. Rouleau as director

- “Harvard model” clinical research program
  - “register” trial patients at the Neuro
  - Study visits occur at the Neuro, followed for care elsewhere
QUESTIONS??

Thank you!!

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