Spinal Muscular Atrophy in 2017

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Disclosures

• MDA Care Center - Grant
• In this presentation, there are slides from both Sarepta Therapeutics and Biogen
• Parent Project Muscular Dystrophy Certified Care Center - Research Liaison Grant
• Local site for Sarepta Exon Skipping Trials 45 and 53
• PI for Santhera Idebenone study
• Medical Advisory Board Marathon Therapeutics
  – No personal honorarium payment received; did not partake in their snacks or wine
• Medical Advisory Board PTC Therapeutics
  – No personal honorarium payment received; honorarium redirected as a contribution to the neurology resident education fund
Objectives

• Review Spinal Muscular Atrophy
• Discuss Nusinersen (Spinraza)
• Discuss Gene Therapy for Spinal Muscular Atrophy
Review of the Genetics of SMA

- SMN1 and SMN2 are found on the 5\textsuperscript{th} chromosome
- There are other forms of spinal muscular atrophy that will not be covered
Autosomal Recessive Inheritance (Both Parents Carriers)

Carrier Father: Rr
Carrier Mother: Rr

Offspring:
- RR: Normal (25%)
- Rr: Carrier (50%)
- rr: Affected (25%)
Clinical Spectrum of SMA
Orthopedic Care

- Unique challenges in this population; different for the different SMA forms
  - Hip subluxation
  - Contractures
  - Scoliosis (type 2)
  - Hypermobility (type 3)
Orthopedic Care

• Special scales exist for the abilities in patients with SMA

• Interventions
  – Bracing
  – Mobility
The Clinical Trials

- Cherish - for type 2 SMA, Phase 3
- Endear - for type 1 SMA, Phase 3
- Embrace - “catch all trial”, Phase 2
- Nurture - pre-symptomatic newborns, Phase 2
  - Can have 2 - 3 copies of SMN2
  - This is a key study on the importance of prenatal screening and newborn screening
**SMN1 gene**\(^{3,6,7}\)

The SMN1 gene is located on chromosome 5q13

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**SMN1 mRNA**

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100% Full-length functional SMN protein

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[https://www.togetherinsma-hcp.com](https://www.togetherinsma-hcp.com)
Spinal Muscular Atrophy - Genetics

- SMN2 is a modifier gene also present on 5q
- Almost identical to SMN1, only 5 nucleotides different
  - C>T nucleotide change in SMN2 creates an exonic splicing suppressor (ESS) that leads to skipping of exon 7 during transcription
- SMN2 usually produces a truncated, non-functional, rapidly degrading, unstable protein
- 10-15% of the time, SMN2 includes exon 7
  - Gene product is identical to SMN1 transcript and is functional
  - Disease severity in SMA is inversely correlated with SMN2 gene copy number
SMN2 gene$^{2,7}$

A C-to-T transition occurs, creating an exonic splicing suppressor (ESS) that leads to a skipping of exon 7

Full-length SMN mRNA

$1 \ 2a \ 2b \ 3 \ 4 \ 5 \ 6 \ 7 \ 8$

~10% Full-length functional SMN protein

Open Circle

Δ7 SMN mRNA

$1 \ 2a \ 2b \ 3 \ 4 \ 5 \ 6 \ 8$

~90% Truncated non-functional SMN protein

Closed Circles
Nusinersen versus Sham Control in Infantile-Onset Spinal Muscular Atrophy

Nusinersen (Spinraza)

- Double blind placebo controlled trial 2:1
- 121 patients <7 months of age at the first dose
  - 80 treated, 41 controls
- All patients had to be symptomatic <6 months of age without ability to sit
- All patients had to have 0 copies SMN1 and 2 copies SMN2
- Planned for about a year (13 months)
- About 80 patients were evaluated in the interim
  - Because of the interim results, all patients started to get drug
Nusinersen (Spinraza)

- Patients could not be trach/vent dependent
- G-tubes were OK
- Hammersmith Infant Neurological Examination
Nusinersen (Spinraza) - HINE

**Grasp:** none, whole hand, immature, pincer
**Kick:** none, horizontal (no lift), vertical, touches leg, touches toes
**Head Control:** unable, wobbles, upright
**Rolling:** none, to side, prone to supine, supine to prone
**Sitting:** none, hip support, props, stable, pivots
**Crawling:** none, elbows, outstretched hands, crawling flat on abdomen, on hands and feet
**Standing:** doesn’t support weight, supports weight, stands with support, stands unassisted
**Walking:** none, bouncing, cruising, walking independently
Nusinersen (interim results)
Nusinersen (final results)
Nusinersen (CHERISH)

- Phase III multi-center trial
- 2 to 12 years
- Symptoms > 6 months at diagnosis
- Hammersmith Functional Motor Scale - Expanded
- Life expectancy greater than 2 years
- Primary endpoint is change from the HFSME baseline of which 3 points is considered significant
- The treatment group gained significantly more function than the untreated group.
What is measured in the HFMSE?

Chair sitting
Long sitting
One hand to head
Sitting, two hands to head
Supine to lying
Prone to supine right
Prone to supine left
Supine to prone left
Supine to prone left
Sitting to lying
Props on forearms
Prop on extended arms
Lifts head from prone
Lying to sitting
Four point kneeling
Crawling
Lift head from supine
Supported standing
Stand unsupported

Stepping
Right hip flexion in supine
Left hip flexion in supine
High kneeling to right half knee
High kneeling to left half knee
High kneeling to stand right
High kneeling to stand left
Stand to sitting on floor
Squat
Jumps 12 inches forward
Ascends 4 stairs with rail
Descends 4 stairs with rail
Ascends 4 stairs without rail
Descends 4 stairs without rail

Each is graded 0-2 with maximum score 66
Nurture Trial
Bertini (2016)

- Open label, multi-center, multi-national
- < 6 weeks before the 1\textsuperscript{st} dose
Nurture Trial

• At 13 months, all infants were alive
• No infants required invasive ventilation, tracheostomy, or non-invasive ventilation >6 hours a day, 7 days a week
• 9/13 full head control
• 5/13 could now sit
• 3/13 could stand with support
• 1/13 walked
• Safety upheld - no one dropped out of the study because of side effects
• Of the studies, the Nurture trial also demonstrated the highest gain in function
• There is further information on this trial but is not yet public
Nusinersen (Spinraza)

• Submitted for NDA
  November 7, 2016

• Approved for use by
  the FDA on December
  23, 2016
Nusinersen

- Indicated for all types of chromosome 5 SMN related SMA
- Given intrathecally
  - Same does for everyone
- Loading Dose
  - Once every 2 weeks x 3
  - 4th dose in 30 days
# Nusinersen side effects

## Table 1. Adverse Reactions that Occurred in at Least 5% of SPINRAZA Patients and Occurred at Least 5% More Frequently or At Least 2 Times as Frequently Than in Control Patients in the Controlled Study in Infants with Symptomatic SMA

<table>
<thead>
<tr>
<th>Adverse Reactions</th>
<th>SPINRAZA 12 mg(^1) N=80</th>
<th>Sham-Procedure Control N=41</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Lower respiratory infection(^2)</td>
<td>43</td>
<td>29</td>
</tr>
<tr>
<td>Upper respiratory infection(^3)</td>
<td>39</td>
<td>34</td>
</tr>
<tr>
<td>Constipation</td>
<td>30</td>
<td>22</td>
</tr>
<tr>
<td>Teething</td>
<td>14</td>
<td>7</td>
</tr>
<tr>
<td>Upper respiratory tract congestion</td>
<td>6</td>
<td>2</td>
</tr>
<tr>
<td>Aspiration</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Ear infection</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Scoliosis</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

1 Data listing doses followed by 12 mg (3 mL) once every 4 months
2 Includes pneumonia, bronchiolitis, pneumonia viral, respiratory syncytial virus bronchiolitis, lower respiratory tract infection, pneumonitis bacterial, bronchiolitis, bronchiolitis viral, pneumonia norwalkella, pneumonia parainfluenza viral, lower respiratory tract infection viral, lung infection, pneumonitis influenza, pneumonitis pseudomembranous, pneumonitis respiratory syncytial viral
3 Includes upper respiratory tract infections, nasopharyngitis, rhinitis, pharyngitis, or tonsillitis
Nusinersen Cost

- $125,000 per vial
- $750,000 for the first year
- $375,000 for the subsequent years
Buy and Bill did not work for CHLA

- There is a significant financial risk
  - CHLA would have to shell out approximately 21 million for the first year to accommodate our patients population
  - The budget for Neurology (one division) is a lot less than that
  - Alternative was offered - Specialty Pharmacy
Single-Dose Gene-Replacement Therapy for Spinal Muscular Atrophy

Single-Dose Gene Replacement Therapy for SMA1

- 15 patients
- AAV 9 cDNA encoding SMN protein
- 3 low dose; 12 high dose
- Primary outcome = safety
- Secondary outcome = time to death or permanent ventilatory support
- CHOP Intend (scored from 0 to 64)
At 20 months, all patients gained milestones.

Table 2. Event-free Survival and Motor and Other Milestones among the 12 Patients in Cohort 2.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age at Study Entry</th>
<th>Event-free Survival</th>
<th>Motor Milestones</th>
<th>Other Achievements</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mo</td>
<td></td>
<td>Brings Hand to Mouth</td>
<td>Controls Head</td>
</tr>
<tr>
<td>4</td>
<td>5.6</td>
<td>31.1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>4.2</td>
<td>28.5</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>1.9</td>
<td>26.1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>7</td>
<td>3.6</td>
<td>28.1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>8</td>
<td>7.9</td>
<td>32.4</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>4.9</td>
<td>28.9</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>10</td>
<td>0.9</td>
<td>25.3</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>11</td>
<td>2.3</td>
<td>23.8</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>12</td>
<td>2.6</td>
<td>23.9</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>13</td>
<td>0.9</td>
<td>22.1</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>14</td>
<td>4.1</td>
<td>22.0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>15</td>
<td>2.1</td>
<td>20.6</td>
<td>+</td>
<td>+</td>
</tr>
</tbody>
</table>

Patients with outcome (%)

<table>
<thead>
<tr>
<th>This study</th>
<th>100</th>
<th>100</th>
<th>92</th>
<th>75</th>
<th>92</th>
<th>92</th>
<th>83</th>
<th>75</th>
<th>92</th>
<th>92</th>
<th>58</th>
<th>50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Natural-history studies</td>
<td>8 by 20 mo</td>
<td>NA</td>
<td>0</td>
<td>0**</td>
<td>0**</td>
<td>0**</td>
<td>0**</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>8 by 20 mo</td>
<td></td>
</tr>
</tbody>
</table>
SUNFISH Phase 2 Trial Part 1 - RG7916

- Double-blind, placebo controlled trial in ambulatory and non-ambulatory patients with SMA 2/3
- Orally administered “small molecule”
  - Mechanism: forces alternative splicing of SMN2
  - Results in expression of full SMN2 mRNA transcript and SMN protein
- Interim analysis of 4 cohorts treated with RG7916 for ≥28 days demonstrated an exposure-dependent increase in SMN protein
  - Up to a median of 2.5-fold increase in SMN protein
- Well tolerated without side effects
- SUNFISH part 2: 150 non-ambulatory patients
  - Safety and efficacy of the dose level selected in part 1
Summary

- Spinal Muscular Atrophy (SMA) has various clinical presentations
- Patients with SMA require multidisciplinary care
- Nusinersen (Spinraza) is an anti-sense oligonucleotide treatment that is now FDA approved with impressive study results
- There is promise in an oral medication for SMA
- A new gene therapy is in the process of development/clinical trials also shows incredible promise
• https://www.uptodate.com/contents/spinal-muscular-atrophy
• http://neuromuscular.wustl.edu/
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