Spinal Muscular Atrophy: Therapeutic Update

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Outline

• Approach to “Floppy Baby”
• Spinal Muscular Atrophy Introduction
• Clinical Management and New Therapies
Floppy Baby

Hypotonia (decreased muscle tone)

Differential Diagnosis?
Hypotonia

Definitions

**Tone**: resistance of muscles to stretch

**Hypotonia**: diminished resistance of muscles to passive stretching)

**Weakness**: diminished muscle power or strength

While weak infants are always hypotonic, infants with hypotonia are not always weak.
Figure 1: Identifying children with motor delays: an algorithm for surveillance and screening.
8. High, Normal, or Low Tone?
   - High: Consider Neuroimaging
   - Normal/Low: Measure CK & TSH

9a. Consider Neuroimaging
9b. Measure CK & TSH

7. Are the History or Exam Results Concerning?
   - Yes: Refer to Early Intervention/Child Find & Consult/Refer to Appropriate Pediatrics Subspecialists
   - No: Continue with neuroimaging assessment

10. Refer to Early Intervention/Child Find & Consult/Refer to Appropriate Pediatrics Subspecialists
Spinal Muscular Atrophy

- Weakness
- Muscle Wasting
- Degeneration of anterior horn cells of spinal cord and brainstem motor nuclei
Classification

• SMA 1: infantile, Werdnig-Hoffman
  – Most common, most severe
  – Prenatal decreased movements (Type 0)
  – Often fatal in first year
• SMA 2: intermediate: reach sitting
• SMA 3: may ambulate for a period
• SMA 4: adult-onset
Epidemiology

- 1 in 6,700 to 10,000 live births worldwide
- 30,000-35,000 in US, Europe and Japan
- 1 in 50 is a carrier
- When both parents carriers, 1 in 4 chance child will have SMA.
Genetics

- Loss or mutation in SMN1 gene
- Leads to decrease in SMN protein
- SMN is critical to health and survival of nerve cells in spinal cord
Autosomal recessive (5q-SMA) (1.7% de novo)

- Deletions or mutations in SMN1 gene on 5q13.2
  - 94% homozygous deletion of exon 7
- SMN protein plays a role in mRNA synthesis in motor neurons
  - Level of SMN protein correlates with disease severity
Physical Manifestations

- Symmetric proximal muscle weakness
  - Lower > Upper
- Absent deep tendon reflexes
- Infants have severe symmetric flaccid paralysis
- Upper cranial nerves spared
- Weak cry, poor suck/swallow, aspiration
- Tongue fasciculations
Physical Manifestations- SMA 0/1

- Arthrogryposis: multiple joint contractures
- Fetal Hypokinesia Deformation Sequence
  - Polyhydramnios
  - IUGR
  - Skeletal abnormalities
  - Multiple articular contractures
  - Pulmonary hypoplasia
Physical Manifestations

- Normal cognitive function
- Progressive weakness
- Decreased endurance
- Limb contractures
- Spine deformity
- Decreased pulmonary function
Progression

- Restrictive respiratory insufficiency
  - Intercostal muscles > diaphragm
  - Paradoxical breathing: ribs in, abd out, bell-shaped chest deformity
- Heart not affected
- Scoliosis
- Weakness
- Life expectancy for Type 1 is <2 years
Management

• Supportive

Consensus Statement for Standard of Care in Spinal Muscular Atrophy

Ching H. Wang, MD, PhD, Richard S. Finkel, MD, Enrique S. Bertini, MD, Mary Schroth, MD, Anita Simonds, MD, Brenda Wong, MD, Annie Aloysius, MRCSLT, HPC, Leslie Morrison, MD, Marion Main, MCSP, MA, Thomas O. Crawford, MD, Anthony Treba, BS, and Participants of the International Conference on SMA Standard of Care

Spinal muscular atrophy is a neurodegenerative disease that requires multidisciplinary medical care. Recent progress in the understanding of molecular pathogenesis of spinal muscular atrophy and advances in medical technology have not been matched by similar developments in the care for spinal muscular atrophy patients. Variations in medical practice coupled with differences in family resources and values have resulted in variable clinical outcomes that are likely to compromise valid measures of treatment effects during clinical trials. The International Standard of Care Committee for Spinal Muscular Atrophy was formed in 2005, with a goal of establishing practice guidelines for clinical care of these patients. The 12 core committee members worked with more than 60 spinal muscular atrophy experts in the field through conference calls, e-mail communications, a Delphi survey, and 2 in-person meetings to achieve consensus on 5 care areas: diagnostic/new interventions, pulmonary, gastrointestinal/nutrition, orthopedics/rehabilitation, and palliative care. Consensus was achieved on several topics related to common medical problems in spinal muscular atrophy, diagnostic strategies, recommendations for assessment and monitoring, and therapeutic interventions in each care area. A consensus statement was drafted to address the 5 care areas according to 3 functional levels of the patient: nonambulatory, sitter, and walker. The committee also identified several medical practices lacking consensus and warranting further investigation. It is the authors’ intention that this document be used as a guideline, not as a practice standard for their care. A practice standard for spinal muscular atrophy is urgently needed to help with the multidisciplinary care of these patients.

Keywords: spinal muscular atrophy; standard of care; consensus statement

Current Problems in the Medical Care of Patients With Spinal Muscular Atrophy

Spinal muscular atrophy is a recessively inherited neuromuscular disease characterized by degeneration of spinal cord motor neurons, resulting in progressive muscular atrophy and weakness. The clinical spectrum of spinal muscular atrophy ranges from early infant death to normal adult life with only mild weakness. These patients often require comprehensive medical care involving multiple disciplines. There is, however, no published practice standard for the care of these patients. Disparity in family resources, medical practitioners’ knowledge, and regional and cultural standards can...
First ever approved therapy for SMA.
Check out our news section for the latest updates on this important milestone.

Learn More

FDA has Approved Spinraza for SMA

Latest News

January 13, 2017
Biogen Presents New ENDEAR Data Showing SPINRAZA (nusinersen) Significantly Reduces Risk of Death or Permanent Ventilation

Biogen presented new data from the Phase 3 ENDEAR study of SPINRAZA™ (nusinersen), which demonstrated...
SMA DRUG PIPELINE

We’re funding and directing research with more breadth and depth than ever before. We know what we need to do to develop and deliver new therapies, which could also work in combination, to reach our goal of treatments for all ages and types. And we’re on the verge of further breakthroughs that will continue to change the course of SMA for everyone affected, and eventually lead to a cure.

IND = Investigational New Drug  NDA = New Drug Application  Last updated: June 2019
Nusinersen/Spinraza

Antisense oligonucleotide

www.spinraza.com
Nusinersen/Spinraza (!!)

- Antisense oligonucleotide
- Binds the SMN2 pre-mRNA
- Increases the rate of inclusion of Exon 7 by displacing splicing proteins
- More SMN2 will be full-length and functional, conceptually decreasing clinical manifestations of SMA

www.spinraza.com
Nusinersen

- Alter the splicing of SMN2, to increase production of fully functional SMN protein
- Orphan drug status
Spinal Muscular Atrophy
Spinal Muscular Atrophy

Long-term improvement in CS3A (infantile-onset SMA) vs. improvement for nusinersen vs. sham procedure control in ENDEAR interim analysis (infantile-onset SMA; 2 SMN2 copies)
Spinal Muscular Atrophy

![Graph showing improvement in milestone scores over time for different conditions and treatments.](image)

- **Largest improvement in NURTURE** (presymptomatic infantile-onset SMA; 2 or 3 SMN2 copies)
- **Long-term improvement in CS3A** (infantile-onset SMA)
- **Improvement for nusinersen vs. sham procedure control in ENDEAR interim analysis** (infantile-onset SMA; 2 SMN2 copies)

*University of Virginia Children's Hospital*
AVXS-101 (Zolgensma)

- AAV-9 viral vector based gene therapy
- 1 time IV injection
- Approval based on clinical efficacy in children with 2 copies of SMN2 gene
AVXS-101 (Zolgensma)

• Start Trial: 3 patients with lower dose
  – 12 patients with higher dose - these all lived 24 months without ventilatory support

• Strive Trial: ongoing
  – 21 patients - 19 still following. Elevated LFTs
AVXS-101 (Onasemnogene Abeparvovec) for SMA1: Comparative Study with a Prospective Natural History Cohort

Abstract

Background: Spinal muscular atrophy type 1 (SMA1) is the leading genetic cause of infant mortality for which therapies, including AVXS-101 (onasemnogene abeparvovec, Zolgensma) gene replacement therapy, are emerging.

Objective: This study evaluated the effectiveness of AVXS-101 in infants with spinal muscular atrophy type 1 (SMA1) compared with a prospective natural history cohort and a cohort of healthy infants.

Methods: Twelve SMA1 infants received the proposed therapeutic dose of AVXS-101 (NCT02122952). Where possible, the following outcomes were compared with a natural history cohort of SMA1 infants (n = 16) and healthy infants (n = 27) enrolled in the NeuroNEXT (NN101) study (NCT01736553): event-free survival, CHOP-INTEND scores, motor milestone achievements, compound muscle action potential (CMAP), and adverse events.

Results: Baseline characteristics of SMA1 infants in the AVXS-101 and NN101 studies were profile. The proportion of AVXS-101–treated infants who survived by 24 months of follow-up...
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AVXS-101 (n = 12)</th>
<th>NN101 - SMA1 (n = 16)</th>
<th>NN101 - healthy (n = 27)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female, n (%)</td>
<td>7 (58)</td>
<td>8 (50)</td>
<td>14 (52)</td>
</tr>
<tr>
<td>Age at first visit (mos)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.9 (2)*</td>
<td>4.0 (2)</td>
<td>3.4 (2)</td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>0.4–7.3</td>
<td>0.4–6.0</td>
<td>0.6–6.1</td>
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<tr>
<td>Age at dosing (mos)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>3.4 (2)</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>0.9–7.9</td>
<td>Not applicable</td>
<td>Not applicable</td>
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<tr>
<td>Race, n (%)</td>
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<tr>
<td>White/not Hispanic or Latino</td>
<td>11 (92)</td>
<td>15 (94)</td>
<td>21 (78)</td>
</tr>
<tr>
<td>Ethnicity, n (%)</td>
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<tr>
<td>White/non-Hispanic</td>
<td>10 (83)</td>
<td>11 (69)</td>
<td>24 (89)</td>
</tr>
<tr>
<td>Age at SMA1 onset (mos)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.4 (1.0)</td>
<td>Not collected*</td>
<td>Not applicable</td>
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<tr>
<td>Minimum–maximum</td>
<td>0.0–3.0</td>
<td>Not applicable</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Did not require support of, n (%)</td>
<td></td>
<td></td>
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<tr>
<td>Nutrition</td>
<td>7 (58)</td>
<td>9 (56)</td>
<td>26 (96)</td>
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<tr>
<td>Non-invasive ventilation</td>
<td>10 (83)</td>
<td>10 (63)</td>
<td>25 (93)</td>
</tr>
<tr>
<td>CHOP-INTEND score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>28.2 (12.3)</td>
<td>20.3 (7.3)</td>
<td>51.1 (8.9)</td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>12.0–50.0</td>
<td>10.0–33.0</td>
<td>32.0–62.0</td>
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<tr>
<td>Ulnar CMAP peak area (mV/s)</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>1.7 (2.1)</td>
<td>1.1 (2.3)</td>
<td>11.6 (4.8)</td>
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<tr>
<td>Minimum–maximum</td>
<td>0.3–7.3</td>
<td>0.0–9.2</td>
<td>1.1–20.4</td>
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<tr>
<td>Ulnar CMAP amplitude (mV)</td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>0.74 (1.07)</td>
<td>0.48 (1.05)</td>
<td>5.54 (1.96)</td>
</tr>
<tr>
<td>Minimum–maximum</td>
<td>0.1–3.4</td>
<td>0.0–4.2</td>
<td>0.5–9.9</td>
</tr>
</tbody>
</table>

CHOP-INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders; CMAP, compound muscle action potential; SD, standard deviation; SMA1, spinal muscular atrophy type 1.

*In the AVXS-101 study, this reflects age at enrollment. Exact age was not collected. However, age rounded to month was recorded and is reported in Table 2. In the NN101 study, use of nutritional support was not documented. However, difficulty swallowing was documented and an affirmation of this was used as a proxy for use of nutritional support.
Fig. 2. Motor function analysis of the AVXS-101 and NN101 studies. (A) Maximum longitudinal CHOP-INTEND scores reached. Mean CHOP-INTEND scores by infant age are shown; shaded areas indicate the standard deviation for each mean at each study visit. (B) Change in longitudinal CHOP-INTEND score up to 24 months of age. CHOP-INTEND, Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders. SD, standard deviation; SMA1, spinal muscular atrophy type 1.
Community Statement from Genentech: FDA Grants Priority Review to Risdiplam for Spinal Muscular Atrophy

November 25th, 2019 | Front Page News

Genentech, a member of the Roche Group, today announced that the U.S. Food and Drug Administration (FDA) has accepted the New Drug Application (NDA) and granted Priority Review for risdiplam, an investigational survival motor neuron-2 (SMN-2) splicing modifier for spinal muscular atrophy (SMA). If approved, risdiplam, an orally administered liquid, would be the first at-home administered medicine for people living with SMA. Below please find a community statement from Genentech.

Dear SMA community,

As part of our ongoing partnership, and following your request to receive important and timely information about the risdiplam clinical development program, we would like to provide an update regarding the regulatory status of our investigational medicine, risdiplam.

The U.S. Food and Drug Administration (FDA) has accepted the filing of the New Drug Application (NDA) for risdiplam for the proposed use in people living with spinal muscular atrophy (SMA). The FDA has granted the application a Priority Review, which means that the agency is currently expected to review the application within 6 months instead of the standard 10 months. The FDA is expected to decide on approval by May 24, 2020.
Risdiplam: Roche and Genentech

**CHOP-INTEND score:** Individual patient plots showed continuous improvement from baseline with risdiplam

Multidisciplinary Care

Neurodevelopmental Therapy
Physical Therapy
Occupational Therapy
Speech/Language/Feeding Therapy
Orthopedics
Pulmonology
Endocrinology
P&O
Multidisciplinary Care

- Pain
- Wounds
- Equipment
Developmental Assessment

- Overall Cognition
- Learning
- Daily Function
- Independence
Coordination of Care

- Referral to subspecialists
- Interpretation of results
- Referral for resources
- Education
  - Genetic counseling
  - Resources available
Thank you!