Spinal Muscular Atrophy: Importance of early diagnosis, management and new treatment options—and outcomes.

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BC Pediatric Society
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Objectives

• 1. Understand SMA and the importance of early diagnosis
• 2. Understand importance of Standards of care
• 3. Discuss new treatment options, accessibility and expectations
• 4. What difference does this mean to outcome
• Disclosures

• Clinical Trials
  • DMD: ReveraGen Pfizer, PTC, Italfarmico, Sarepta
  • SMA: Biogen/IONIS Pharmaceuticals,
  • National Advisory Consultant Biogen and Novartis for SMA
  • Any photos not in the public domain have been consented by the family
  • Educational material for Roche, Novartis and Biogen
About SMA
5q: Spinal Muscular Atrophy

- An inherited progressive neuromuscular disorder (AR)
- Caused by a defect of the SMN1 gene on Chromosome 5q
- Incidence ~1/10-11,000
- Carrier rate 1/40-60 : Leading cause of infant mortality
- Degeneration of the motor neurones in the spinal cord with progressive weakness and paralysis
- Untreated infants with type 1 SMA do not achieve motor milestones and die before the age of 2 years from respiratory failure
  - SMA type 1 non sitters
  - SMA type 2 sitters
  - SMA type 3 walkers
  - SMA type 4 Adult onset
- Potential for change of Phenotype
Genetics of SMA

- 2 main genes
  - **SMN1 gene** produces a fully functional protein
  - Mutations SMN1 gene cause SMA
  - 98% homozygous deletion of Exon7/8 SMN1 gene

- **SMN2 gene** differs from SMN1 gene by 1 nucleotide
  - 10% of SMN2 transcripts contain exon 7
  - Most of SMN2 lacks exon 7 and produces an inferior unstable protein which rapidly degrades
  - Greater no. of SMN2 copies the milder the disease
SMA: Phenotypes

Classification
Advances in treatment of SMA–New Phenotypes, New Challenges, New Implications for Care
Schorling, D., Pechmann, A., & Kirschner, J.

Age at onset of symptoms

<table>
<thead>
<tr>
<th>SMN2 copy number(s)</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>≥5</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA type #</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milestones achieved</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical presentation</td>
<td>no Sitting</td>
<td>sitting, no walking</td>
<td>independent walking</td>
<td>independent walking</td>
<td></td>
</tr>
<tr>
<td></td>
<td>„floppy infant“ difficulties in breathing and coughing, difficulties in swallowing, fasciculations of tongue</td>
<td>delay in motor development, weakness, difficulties in coughing, joint contractures, scoliosis</td>
<td>variable degree of weakness, joint contractures, scoliosis, loss of ambulation</td>
<td>variable, but milder weakness</td>
<td></td>
</tr>
</tbody>
</table>

SMA 1  58%
SMA 2  29%
SMA 3  13%
SMA 4  1-2%
SMA classification

- **New SMA classification**
  - **Type 0**
    - Non-sitters
  - **Type 1**
    - Sitters
  - **Type 2**
    - Ambulant
  - **Type 3**
  - **Type 4**

- **Original SMA classification**

**SMN2 copy number**:

- Type 0:
  - 1: 7%
  - 2: 20%
  - 3: <1%
  - 4: <1%

- Type 1:
  - 1: <1%
  - 2: 16%
  - 3: 5%
  - 4: <1%
  - >4: 78%

- Type 2:
  - 1: 0%
  - 2: 5%
  - 3: 49%
  - 4: 44%
  - >4: 2%

- Type 3:
  - 1: 0%
  - 2: 4%
  - 3: 4%
  - 4: 0%
  - >4: 81%

- Type 4:
  - 1: 11%
  - 2: 0%
  - 3: 0%
  - 4: <1%
  - >4: 0%
Natural History of SMA type 1

Observational Study of SMA type 1: Finkel et al Neurology August 26, 2014 810-817

More than 90% of SMA Type 1 patients will not survive or will need permanent ventilation support by age 2

- 75% survival 8.1 mos
- 50% survival 10.5 mos
- 50% survival 8 mos
- 25% survival 13.6 mos
- 8% survival 20 mos

Milestone for a healthy infant
- Milestone for SMA Type 1 survival rates per Finkel
- SMA Type 1 survival rate per Kolb

Climbs furniture alone; hits and throws a ball
Walks alone; may run and walk up steps; eats with a spoon
Cruises may stand alone
Rolls over in both directions
Holds head steady above; brings hands to mouth

Symptoms may present
- "Flappy baby" syndrome
- Muscle weakness (legs more than arms)
- Poor head control
- Bulbar muscle weakness (weak cry, difficulty swallowing, aspiration)
- Will never sit unsupported

PhCR (Finkel)
NeuroNEXT (Kolb)
# Diagnostic journey in Spinal Muscular Atrophy: Is it still an odyssey?


First symptoms identified

<table>
<thead>
<tr>
<th></th>
<th>SMA I (n=191)</th>
<th></th>
<th>SMA II (n=210)</th>
<th></th>
<th>SMA III (n=80)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>First symptoms identified</td>
<td>N</td>
<td>%</td>
<td>First symptoms identified</td>
<td>N</td>
<td>%</td>
<td>First symptoms identified</td>
</tr>
<tr>
<td>Hypotonia (general)</td>
<td>113</td>
<td>59.16%</td>
<td>Not acquired standing position</td>
<td>83</td>
<td>39.52%</td>
<td>Unsteady ambulation</td>
</tr>
<tr>
<td>Developmental delay (head control)</td>
<td>33</td>
<td>17.28%</td>
<td>Developmental delay (sitting position)</td>
<td>43</td>
<td>20.48%</td>
<td>Frequent falls</td>
</tr>
<tr>
<td>Absence of antigravitary movements</td>
<td>15</td>
<td>7.85%</td>
<td>Hypotonia (lower limbs)</td>
<td>38</td>
<td>18.10%</td>
<td>Difficulty in rise from the floor</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>15</td>
<td>7.85%</td>
<td>Not acquired crawling in time</td>
<td>4</td>
<td>1.90%</td>
<td>Difficulty in stair’s climbing</td>
</tr>
<tr>
<td>Developmental regression</td>
<td>7</td>
<td>3.66%</td>
<td>Failure to thrive</td>
<td>1</td>
<td>0.48%</td>
<td>Developmental delay</td>
</tr>
<tr>
<td>Feeding related problems</td>
<td>6</td>
<td>3.14%</td>
<td>Respiratory infections</td>
<td>1</td>
<td>0.48%</td>
<td>Developmental regression</td>
</tr>
<tr>
<td>Absence of deep tenden reflexes</td>
<td>2</td>
<td>1.05%</td>
<td></td>
<td></td>
<td></td>
<td>’Clumsy’ movements</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Running difficulties</td>
<td>3</td>
<td>3.75%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Muscle Weakness</td>
<td>2</td>
<td>2.50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Toe walking</td>
<td>2</td>
<td>2.50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Accidental finding</td>
<td>2</td>
<td>2.50%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Tremor</td>
<td>1</td>
<td>1.25%</td>
<td></td>
</tr>
</tbody>
</table>

https://doi.org/10.1371/journal.pone.0230677.t001
Trajectory of SMA
Delay in Diagnosis:

- Diagnostic delay is common in SMA
- The length of delay varied by SMA type
- New Born Screening would help to end diagnostic delay
Importance of standards of care and new treatment options—disease modifying therapies

- SOC guidelines
- Improved respiratory care
- Nutritional care
- Orthopedic care
- Physiotherapy
- Disease modifying therapies (DMT)
- What are the prognosticators and what has changed
- Approvals of Nusinersen, onasemnogene abeparvovec, and Risdiplam
Therapeutic Approaches

- Modify Splicing of SMN2
- Replacing the SMN1 gene
- Upregulating muscle growth
3 Possible Treatments —

- 3 drugs approved Health Canada
- BUT only nusinersen funding plan in place in the provinces

**SMA Treatment Considerations**

- **Nusinersen (IT)**
  - Onasemnogene Abeparvovec (IV)
  - Risdiplam (PO)

**Administration**

- Nusinersen administered as loading-dose and then on 4-month schedule thereafter
  - Post-lumbar puncture syndrome
  - Administration is difficult in young patients

- Approved gene therapy onasemnogene abeparvovec needs single administration
  - Ongoing monitoring and steroids may be required

- Investigational agent risdiplam administered once daily
  - Potential at-home treatment
  - Safety still being studied, although no new safety signals reported

**Infusion**

**Liquid oral**
Nusinersen

- First drug approved for 5q SMA treatment in Canada during June 2017
- Antisense oligonucleotide administered IT
- Enhances the inclusion of exon 7 in mRNA transcripts of SMN2
- Results in increased production of a full length SMN protein
- After 4 initial loading doses, injected IT every 4 months
HINE Motor Milestone Scores Over Time Across Studies

Parsons et al, CureSMA 2019, Platform Presentation
<table>
<thead>
<tr>
<th>Motor milestone</th>
<th>Expected age of achievement in healthy infants 1st-99th percentile</th>
<th>Caregiver-reported site-confirmed achievement in NURTURE participants</th>
<th>Median (95% CI) age of first achievement, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sitting without support</td>
<td>3.8–9.2 months</td>
<td>3 SMN2 copies: 10/10 (100%)</td>
<td>6.4 (5.1–7.9)</td>
</tr>
<tr>
<td>Standing with assistance</td>
<td>4.8–11.4 months</td>
<td>2 SMN2 copies: 15/15 (100%)</td>
<td>7.9 (5.9–9.2)</td>
</tr>
<tr>
<td>Hands and knees crawling</td>
<td>5.2–13.5 months</td>
<td>3 SMN2 copies: 10/10 (100%)</td>
<td>8.3 (3.5–9.5)</td>
</tr>
<tr>
<td>2 SMN2 copies: 15/15 (100%)</td>
<td>8.0 (5.1–13.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking with assistance</td>
<td>5.9–13.7 months</td>
<td>3 SMN2 copies: 10/10 (100%)</td>
<td>8.7 (7.2–10.5)</td>
</tr>
<tr>
<td>2 SMN2 copies: 13/15 (87%)</td>
<td>15.5 (8.9–20.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standing alone</td>
<td>6.9–16.9 months</td>
<td>3 SMN2 copies: 10/10 (100%)</td>
<td>9.6 (8.0–11.8)</td>
</tr>
<tr>
<td>2 SMN2 copies: 13/15 (87%)</td>
<td>16.1 (11.8–18.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Walking alone</td>
<td>8.2–17.6 months</td>
<td>3 SMN2 copies: 10/10 (100%)</td>
<td>11.4 (10.3–14.6)</td>
</tr>
<tr>
<td>2 SMN2 copies: 12/15 (80%)</td>
<td>18.6 (12.9–25.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12.3 (11.2–14.9)</td>
</tr>
</tbody>
</table>
Gene Therapy: Onasemnogene Abeparvovec (OA)

OA is a gene therapy designed to deliver a functional copy of the SMN1 gene to motor neuron cells in SMA patients.

Single IV infusion

OA comprises the shell of a genetically engineered virus Adeno-associated virus (AAV) 9, called a capsid, Delivers SMN1 transgene under continuous promotor.

One and Done IV
Dose—according to weight
Approved in USA, Japan and Brazil for children < 2 yr
Recommendations by CADTH for use in SMA with 1-3 copies of SMN2 < 6/12
Approved in EU for SMA with up to and including 3 copies of SMN2 < 21 kg
Onasemnogene Abeparvovec

• Patients treated:

<table>
<thead>
<tr>
<th>Access to dosing:</th>
<th>Ages:</th>
<th>Number treated:</th>
</tr>
</thead>
<tbody>
<tr>
<td>START</td>
<td>SMA type I; &lt; 6 months old</td>
<td>15</td>
</tr>
<tr>
<td>SPR1NT</td>
<td>SMA; pre-symptomatic 2x or 3xSMN2 copies; &lt; 6 weeks old</td>
<td>30</td>
</tr>
<tr>
<td>STRIVE</td>
<td>SMA type I; &lt; 6 months old</td>
<td>33</td>
</tr>
<tr>
<td>STRIVE-EU</td>
<td>SMA type I; &lt; 6 months old</td>
<td>22</td>
</tr>
<tr>
<td>Managed Access Program</td>
<td>SMA; &lt; 2 years old</td>
<td>43 (as of Dec 2019)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
<tr>
<td>Commercial dosing</td>
<td>SMA; &lt; 2 years old</td>
<td>192 (as of Dec 2019)&lt;sup&gt;1&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

• As of June 18 2021, >1200 patients have been treated world-wide<sup>2</sup>

Efficacy: SPR1NT pre-symptomatic treatment

2xSMN2 copy patients
Motor Outcome in Bailey scale
Pre-symptomatic SPRINT

**SPRINT:** OA enabled age-appropriate development of gross motor function

Gross motor scores of patients with 2 copies of **SMN2** (n=14)

Gross motor scores of patients with 3 copies of **SMN2** (n=15)

50% (7/14) of patients with 2 copies of **SMN2** and 100% (15/15) of patients with 3 copies of **SMN2** achieved gross motor scores similar to same-age peers without SMA, as of the Dec 2019 data cut. 

*Gross motor function was measured by the Bayley Scales of Infant and Toddler Development, a standardized, well-accepted tool to assess the development of children between the ages of 1 and 42 months, and compares these scores to a standardized norm.*

1
Presymptomatic treatment (June 2021)

• 100% children treated presymptomatically in the SPRINT 2 copy cohort survived without respiratory or nutritional support
• All children sat independently for > 30 seconds within the normal timeline
• Majority (11/14) went onto stand independently and 9/14 walked independently most within the normal age range
• CHOP intend >58 in 100%

• In **Symptomatic** Children with SMA type 1 82% achieved motor milestones not achieved in the natural history study and 49% sat unsupported
Management of Known Adverse Events

- Hepatitis
- Platelets
- Cardiac

Prophylactic prednisone / prednisolone:

- Pre-treat prednisolone – 1-2 mg/kg/d – beginning *day prior* to onasemnogene abeparvovec infusion
- Prednisolone 1-2 mg/kg/d (x30 days); wean over additional 30 days
- Vomiting, Fever, Thrombocytopenia, Transaminitis, elevation of Troponin I
- 3 reports of Thrombotic Microangiopathy (TMA)
Patient Selection & Preparation

- Effective disease-modifying therapy (not a “cure”)
- Motor neuron loss may begin before birth (may not fully “normalize” phenotype)
- Clinical trials focused on children < 6 months old; “real-world data” is emerging
- Less experience in older children with more severe symptoms
- Careful balance of potential benefits vs. potential side effects
- Evaluate for underlying medical conditions that might heighten risk of side effects
- Need for close & careful monitoring (months) post-dosing
Risdiplam (RG7916): An oral molecule with CNS and peripheral distribution

Risdiplam\textsuperscript{1,2}

- A selective \textit{SMN2} splicing modifier designed to bind uniquely with specificity to \textit{SMN2} pre-mRNA
- Promotes the inclusion of exon 7 in \textit{SMN2} mRNA and the production of full-length \textit{SMN2} mRNA and functional SMN protein
- Orally administered with a systemic distribution
- Liquid once daily
- Penetrates the blood–brain barrier
- Developed in collaboration with SMA Foundation and PTC Therapeutics

DNA, deoxyribonucleic acid; mRNA, messenger ribonucleic acid; SMA, spinal muscular atrophy; SMN, survival of motor neuron.

### Managing SMA: Risdiplam Clinical Trial Programme

<table>
<thead>
<tr>
<th>Trial (NCT)</th>
<th>Design</th>
<th>Type of SMA</th>
<th>Patient Age Range</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAINBOWFISH (NCT03779334)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Open-label, single-arm, multicentre</td>
<td>Presymptomatic</td>
<td>Infant to 6 wk</td>
<td>Recruiting</td>
</tr>
<tr>
<td>FIREFISH (NCT02913482) 2 Parts&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Open-label</td>
<td>Type 1</td>
<td>Infants</td>
<td>Part 2 met primary endpoint: 29% of infants (12/41) sitting without support for 5 sec by month 12&lt;sup&gt;3&lt;/sup&gt;</td>
</tr>
</tbody>
</table>
| SUNFISH (NCT02908685) 2 Parts<sup>4</sup> | Double-blind, PBO-controlled | Type 2 or 3 (nonambulatory) | 2 to 25 y         | Part 2 met primary endpoint: Change from baseline in the Motor Function Measure 32 scale after 1 y with risdiplam vs PBO<sup>5</sup>  
  - No treatment-related safety findings leading to study withdrawal |
| JEWELFISH (NCT03032172) 2 Parts<sup>6</sup> | Open-label, exploratory | Previously treated with SMA-directed therapies | 6 mo to 60 y      | Recruiting           |
FIREFISH Study: Infants 1-7 months Type 1 SMA 2 SMN2 copies

- 41 infants
- Median age of enrollment 5.3 months
- At assessment median age of 20.7 months
- 90% showed > 4 point increase in CHOP intend
- 56% achieved a score > 40 (median increase 20 points)
- 93% were alive
- 85% did not require ventilation or any respiratory support
- 89% were able to feed orally
- 29% could sit > 5 secs at 12 months
- No treatment related safety findings led to drug withdrawal
Risdiplam in type 2 and 3 SMA (sunfish)

• Children and Adults with SMA type 2 and 3 aged 2-25 years had improved motor function and stabilization on MFM 32 score at 24 months
• Increased motor function on RULM
• No new safety concerns
• Good benefit vs risk profile
• More than 2,500 patients now treated
• Real world evidence
• S/E: RTI, pyrexia, headaches, diarrhoea, influenza and pneumonia
Treatment evolution in SMA

**Primary prevention**
- Reproductive carrier screening
- Reproductive options for couples at high risk

**Expected outcomes**
- Reduction in incidence and prevalence of SMA

**Secondary prevention**
- Newborn screening and early treatment

**Expected outcomes**
- Reduction in burden of SMA
- Increase in SMA prevalence
- Evolution of new phenotypes
- Personalized (precision medicine) model of care

**Tertiary prevention**
- Treatment of symptomatic patients

**Expected outcomes**
- Modification of natural history and disability
- Increase in SMA prevalence
- Evolution of new phenotypes
- Increase in proactive care

- Treat all patients with manifesting disease
  - Mainly effect in standard of care and evolving phenotypes

- Treat all pre-symptomatic cases detected by newborn screening
  - Mainly effect in burden and development of the disease

- Perform genetic counseling in all carriers detected in a population based screening
  - Mainly effect in the incidence and prevalence
Now treatment choices-- 3 DMT and SOC

- What does this mean for outcomes
- What treatment should we use and when
- What are the changes in Rehabilitation
- Ensuring SOC
- What about changes in care of backs and hips and feeding and bones and equipment
- What about NB Screening
- Cost
- Combination Therapies?
Prognostic Factors and treatment effect modifiers in SMA causing increased survival

1. SMN2 Copy number
   - Genotype/phenotype is not absolute

2. SMA severity

3. More aggressive SOC – leads to increased survival---however this does not lead to acquisition of motor milestones
What are the **prognosticators** of **outcome** in SMA

- Introduction of Disease Modifying Treatments (DMTs) has changed the course and outcome of SMA - dramatically
- Treated patients live longer and have improved functional abilities
- Patients have improved quality of life
- Prognostic factors include
  - SMN2 copy number
  - Baseline motor, bulbar and respiratory function
  - Age of symptom onset
  - Age at treatment onset
  - Implementation of standards of care
Factors which modify outcomes of treatment

• Disease duration before initiation of DMT
• Age at treatment initiation in SMA types 1, 2 and 3
• Children with SMA 6-15 years are very susceptible to complications such as progressive contractures, scoliosis and this causes functional deterioration.
• Age of Symptom onset
• Supportive therapy
• Disease severity
• Although SMN2 copy number has a prognostic effect in untreated patients it did not lead to a better response to treatment
• Presymptomatic children with 3 copies of SMN2
Conclusions

• Disease Modifying Treatments (DMTs) in SMA are changing the disease trajectory
• Main factors in determining outcome include
  • Age at treatment initiation
  • Use of supportive therapies
  • Disease duration
  • EARLY DIAGNOSIS
  • NewBorn Screening Programs

• Need for Markers to monitor response to ongoing treatment
• Ongoing trials need to ensure adjustments for potential confounders
• Real world evidence and use of Registries-CNDR
Things We Have Learned & Things We Need To Know

- Importance of timing of treatment initiation
- Pre-symptomatic Rx shows favourable outcomes
- New Rx options are changing the natural history and phenotype of SMA
- Longer studies needed to elucidate efficacy and safety profiles and how to individualize therapy
- Do clinical trial populations reflect real world patients?
- How can we improve function with rehabilitation?
- What are the best outcome measures?
- Importance of registries
A Zoom meeting with SMA!