Therapeutic Update on Neuromuscular Disorders

SMA AND DMD

Conference Highlights From 2018
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Therapeutic Update on Neuromuscular Disorders

Conference Highlights from:

• Annual Meeting of the American Academy of Neurology – AAN 2018
• 15th International Congress on Neuromuscular Diseases – ICNMD 2018
• 47th Annual Meeting of the Child Neurology Society – CNS 2018
• 23rd Annual Congress of the World Muscle Society – WMS 2018
Faculty

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Neuromuscular Section Head
Children's Hospital of Philadelphia
Philadelphia, PA, USA
Discussion Outline

Introduction

Therapeutic Update on: Spinal Muscular Atrophy

Therapeutic Update on: Duchenne Muscular Dystrophy
**Introduction**

**SMA**¹,²

- Leading genetic cause of infant mortality
- Caused by mutations in the *SMN1* gene
- Historically classified, based on maximal gross motor function achieved and age of onset, as Type I (onset < 6 months), Type II (onset < 18 months), Type III (onset > 18 months), and Type IV (adult onset)

**DMD**³

- Lethal X-linked recessive neuromuscular disorder
- Caused by mutations in the dystrophin gene

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Diagnosis and Pathophysiology of SMA and DMD

Symptoms of SMA\(^1\)
- Weakness
- Hypotonia
- Respiratory failure
- Tongue fasciculations
- Paradoxical breathing

Symptoms of DMD\(^2\)
- Motor function delay
- Calf pseudohypertrophy
- High CPK levels


CPK, creatine phosphokinase.
Diagnosis and Pathophysiology of SMA and DMD

Confirmation of diagnosis by genetic testing
- Homozygous $SMN1$ deletion in ~ 95% of SMA patients\textsuperscript{1}
- Dystrophin gene deletion (~ 70%), duplications, and micro-mutations/point mutations in DMD patients\textsuperscript{2}

Complications of SMA\textsuperscript{1}
- Respiratory infections
- Feeding problems
- Orthopedic complications

Complications of DMD\textsuperscript{2,3,4}
- Pulmonary failure
- Cardiomyopathy
- Orthopedic complications

2018 Conference Highlights on the Treatment of SMA
Mechanistic Strategies to Treat SMA

**Splicing modification**
Modification of SMN2 mRNA splicing to increase production of functional SMN protein

**Gene replacement**
Replacement of faulty SMN1 gene using viral-vector-based gene therapy

**Muscle activation**
Improvement of muscle force

Nusinersen

- Antisense oligonucleotide SMN2 splicing modifier
- First approved treatment for patients with SMA
- Approved in the USA, Europe, and Japan for the treatment of pediatric and adult patients


\(^a\) All patients with 5q SMA.
Nurture: Presymptomatic SMA

- Phase 2, open-label, single-arm study of nusinersen in infants with genetically diagnosed SMA
- Patients age ≤ 6 weeks at first dose
- Efficacy endpoints:
  - Time to death or respiratory intervention
  - Motor function

Crawford T, et al. Presented at CNS 2018; abstract number 146.
Interim results of the NURTURE study reported that all 25 participating infants were alive.

None of the participants required permanent ventilation.

All participants were able to sit without support and 22 participants were able to walk.

No new safety concerns appeared.

Interim Analysis May 2018.
Newborn Screening

- NURTURE study highlights the importance of early diagnosis\(^1\)
- SMA is part of the RUSP in the USA\(^2\)
- Several US states have already implemented newborn screening for SMA\(^1\)
- Presymptomatic identification of SMA raises the challenge of when to start treatment for the different types of patients classified by *SMN2* copy number\(^3\)

1. Personal communication John Brandsema.
Considerations and Challenges for Newborn Screening

• Patients with < 4 SMN2 copies should be treated immediately
  • Unclear risk:benefit ratio for patients with ≥ 4 copies
  • Lack of biomarkers makes detection of motor neuron damage challenging
  • Early treatment for patients with ≥ 4 copies may be advisable to avoid irreversible damage

• Patients with point mutations will not be detected by newborn screening

Personal communication Basil Darras and John Brandsema.
Nusinersen Open-Label Extension Studies

- SHINE: patients who previously participated in investigational studies with nusinersen
  - Accumulating data regarding long-term treatment effects in patients with SMA Types I–III

Ambulatory Function and Fatigue in Nusinersen-Treated Children With SMA

- 14 patients from CS2/CS12 open label studies:
  - Ambulatory,
  - Nusinersen-treated,
  - Mean age at screening 8.6 years
- Efficacy endpoints:
  - 6MWT
  - Fatigue

Results
- Median distance walked increased by 17 m at Day 253 and by 99 m at Day 1,050 (baseline 250.5 m)
- Median fatigue decreased by 0.1% at Day 253 and by 3.8% at Day 1,050 (baseline 14.8%)

6MWT, 6-minute walk test.
Montes J. et al. Presented at AAN 2018; abstract number P2.322.
Nusinersen Experience in Individuals With SMA Type III: A Case Series

• 11 patients:
  • SMA Type III
  • 3 or 4 copies of SMN2
  • Median age at data cut-off: 14.1 years

Results
• Stabilization or improvement in 6MWT over a long follow-up period
• Higher-functioning patients also benefit
• AEs were consistent with previous experience

AE, adverse event.

Chiriboga C, et al. Presented at CNS 2018; abstract number 60.
Nusinersen Efficacy in Adults With SMA

• Evidence of efficacy in teenage and adult patients with SMA is emerging$^{1,2,3}$
  • Original study population: no adults
• Presentation of single-center experience in adults treated with nusinersen at Stanford University$^1$
  • Comparison with PNCR’s natural history study


PNCR, Pediatric Neuromuscular Clinical Research Network.
Nusinersen Efficacy in Adults With SMA

Single-center experience: Stanford University

• Patients age 18–65 years

Results

• Stabilization or improvement in HFMSE and RULM compared with a decline in natural history study
• Most improvements in respiratory measures (MIP, FVC)
• More data collection required

FVC, forced vital capacity; HFSME, Hammersmith Functional Motor Scale-Expanded; MIP, maximal inspiratory pressure; RULM, Revised Upper Limb Module.

Importance of Real-World Data and Experience

• Patients with very low motor function or severe comorbidities are often excluded from SMA clinical trials
• Functional scales may be challenging to use outside the trial setting
• Improved patient experience may not be reflected in scores on functional scales
• Listening to patient experience is key
Challenges for the Treatment of Adult Patients

- Comorbidities may make intrathecal drug delivery challenging
- Slow functional change may make patients reluctant to take treatment
- Lack of clinical data on treatment of adults made clinical expectations challenging

Personal communication Basil Darras and John Brandsema.
AVXS-101: SMN1 Gene Replacement Therapy

- AAV9-based gene-replacement therapy containing a copy of the human SMN1 gene
- AVXS-101 received Breakthrough Therapy designation and is currently under Priority Review by the FDA
- SAKIGAKE (Japan) and PRIME designations (Europe)
AVXS-101: Phase 1 Data – 24-Month Follow-Up

- Open-label dose-escalation, one-time IV dose
- Minimally effective dose (cohort 1) or proposed therapeutic dose (cohort 2)
- Symptomatic SMA Type I; two SMN2 copies
- Outcome measures:
  - Safety
  - Death or permanent ventilation
  - Ability to sit unassisted
  - Motor function

IV, intravenous.
AVXS-101: Phase 1 Data – 24-Month Follow-Up

• All 15 patients in the study were alive without requiring permanent ventilation 24 months after gene transfer
• Cohort 2: median age 27.8 months at last follow-up
• 11 of 12 patients were able to sit unassisted and could feed orally
• AVXS-101 safety profile of appeared to be favorable

AVXS-101: Phase 1 Data – 24-Month Follow-Up

- CHOP INTEND mean increase at Month 1: 9.8
- CHOP INTEND mean increase at Month 3: 15.4

CHOP INTEND, Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disorders.
• Risdiplam is an orally bioavailable small molecule that distributes centrally and peripherally

<table>
<thead>
<tr>
<th>Trial name</th>
<th>Patients</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIREFISH¹</td>
<td>SMA Type I; age 1–7 months</td>
<td>2/3</td>
</tr>
<tr>
<td>SUNFISH²</td>
<td>SMA Type II, III; age 2–25 years</td>
<td>2/3</td>
</tr>
<tr>
<td>JEWELFISH³</td>
<td>SMA Type II, III; age 6 months–60 years; previously treated with an SMN2-targeting therapy</td>
<td>2</td>
</tr>
</tbody>
</table>

FIREFISH Interim Data: Infantile-Onset SMA

- Multicenter, open-label study,
- Symptomatic SMA Type I

- Results after 8 months of treatment:
  - 90% of infants were alive and event-free
  - 43% were able to sit with or without support and achieved head control
  - 57% achieved a CHOP INTEND score of ≥ 40
  - 93% achieved ≥ 4-point CHOP INTEND increase (clinically meaningful)

The safety profile appeared favorable. The three most common AEs were fever (52.4%), diarrhea (26.8%) and upper respiratory tract infections (19%).
**SUNFISH Interim Data: SMA Type II and III**

- Double-blind, two-part, placebo-controlled trial; SMA Type II and III
- Part 2: safety and efficacy in non-ambulant patients

<table>
<thead>
<tr>
<th>Endpoint (at 12 months of treatment)</th>
<th>&gt; 12 months of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MFM</strong></td>
<td>*<em>All patients (N = 30)</em></td>
</tr>
<tr>
<td>Mean total MFM change from baseline (SD)</td>
<td>2.47 (4.17)</td>
</tr>
<tr>
<td>Median total MFM change from baseline (range)</td>
<td>3.13 (−7.3 to 11.5)</td>
</tr>
<tr>
<td>Proportion of patients who achieved improvement (i.e. a change from baseline in MFM score ≥ 3), % (n)</td>
<td>63.3 (19/30)</td>
</tr>
</tbody>
</table>

*Excludes 4 patients who performed the MFM20 assessment (only patients who performed the full MFM32 assessment are included in the analysis) and 1 patient who had dropped out of the study prior to the Month 12 visit. Data cut-off July 6, 2018.


Current and Emerging SMA Treatments

• New era in terms of SMA treatment
  • There is a disease-modifying therapy
  • There are more options on the horizon
  • The optimal time to treat must be determined

• Combination treatments
  • Phenotype modulators + SMN-targeted therapy may be optimal
  • The feasibility of combination therapy has yet to be determined

Personal communication Basil Darras and John Brandsema.
Treatment Initiation: Further Considerations

• Determining the optimal treatment strategy might depend on the individuals genetic background and predicted phenotype\(^1\)
  • Presymptomatic treatment is likely to be optimal

• Biomarkers may help optimize treatment timing\(^1\)
  • pNF-H is a potential disease-activity and treatment-responsive biomarker
  • pNF-H levels are highest in patients with SMA Type I
  • Treatment with nusinersen appears to decrease pNF-H levels\(^2\)

pNF-H, phosphorylated neurofilament heavy chain.

1. Personal communication Basil Darras and John Brandsema.
2018 Conference Highlights on the Treatment of DMD
Mechanistic Strategies to Treat DMD

• Corticosteroids to decrease inflammation (e.g. prednisone, deflazacort)
• Exon skipping with ASOs to increase dystrophin expression (eteplirsen, golodirsen)
• Targeting RNA translation to increase dystrophin levels (ataluren)
• Gene-replacement therapy (micro-dystrophin)
• Other strategies
Current DMD Treatment Landscape

USA:
- Deflazacort for patients age ≥ 5 years\(^1\)
- Eteplirsen for patients with mutation of the dystrophin gene amenable to exon 51 skipping\(^2\)
  - Conditional approval based on increased dystrophin production

Europe:
- Ataluren for ambulatory patients age ≥ 2 years with nonsense-mutation DMD\(^3\)

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Meta-Analysis of Deflazacort vs Prednisone/Prednisolone

• Post-hoc analysis of the ACT DMD trial:
  • Randomized, double-blind, placebo-controlled 48-week trial
  • Patients with nonsense mutation DMD, age 7–16 years
• Post-hoc analysis of patients in placebo arm who received corticosteroid therapy for ≥ 6 months at study entry and throughout the study
  • Deflazacort (n = 53)
  • Prednisone/prednisolone (n = 61)
• Endpoints included:
  • 6MWD
  • TFT

## Meta-Analysis of Deflazacort vs Prednisone/Prednisolone

### LS mean change (95% CL) from baseline to Week 48

<table>
<thead>
<tr>
<th>Endpoint Δ (SE) (95% CL)</th>
<th>Deflazacort (n = 53)</th>
<th>Prednisone/ prednisolone (n = 61)</th>
<th>In favor of deflazacort</th>
<th>LS mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD, meters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−39.01 (15.05)</td>
<td>−70.59 (13.40)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−68.85 to −9.17)</td>
<td>(−97.16 to −44.02)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TFTs, seconds</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-stair climb</td>
<td>3.79 (1.13)</td>
<td>6.67 (1.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1.54 to 6.03)</td>
<td>(4.69 to 8.64)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-stair descent</td>
<td>3.89 (1.29)</td>
<td>5.66 (1.12)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1.33 to 6.45)</td>
<td>(3.43 to 7.89)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rise from supine</td>
<td>4.50 (1.24)</td>
<td>7.10 (1.13)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2.05 to 6.95)</td>
<td>(4.86 to 9.34)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10-m walk/run</td>
<td>3.16 (0.93)</td>
<td>3.25 (0.85)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(1.32 to 5.00)</td>
<td>(1.56 to 4.94)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSAA total score</td>
<td>−3.39 (0.70)</td>
<td>−4.53 (0.66)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−4.78 to −2.01)</td>
<td>(−5.83 to −3.23)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PODCI</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sport/physical functioning</td>
<td>−4.80 (2.49)</td>
<td>−10.76 (2.25)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−9.73 to −0.13)</td>
<td>(−15.21 to −6.31)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transfers/basic/mobility</td>
<td>−7.53 (2.62)</td>
<td>−9.20 (2.34)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(−12.72 to −2.35)</td>
<td>(−13.84 to −4.57)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Standardized t-statistic

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>In favor of deflazacort</th>
<th>LS mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>6MWD, meters</td>
<td></td>
<td>31.6 (0.2 to 62.9)</td>
</tr>
<tr>
<td>10-m run/walk, seconds</td>
<td>0.1 (−1.9 to 2.1)</td>
<td></td>
</tr>
<tr>
<td>4-stair climb, seconds</td>
<td>2.9 (0.5 to 5.23)</td>
<td></td>
</tr>
<tr>
<td>4-stair descend, seconds</td>
<td>1.8 (−1.0 to 4.5)</td>
<td></td>
</tr>
<tr>
<td>Rise from supine, seconds</td>
<td>2.6 (−0.0 to 5.2)</td>
<td></td>
</tr>
<tr>
<td>NSAA (total)</td>
<td>1.1 (−0.4 to 42.6)</td>
<td></td>
</tr>
<tr>
<td>PODCI (mobility)</td>
<td>1.7 (−3.9 to 7.2)</td>
<td></td>
</tr>
<tr>
<td>PODCI (sports)</td>
<td>6.0 (0.7 to 11.3)</td>
<td></td>
</tr>
<tr>
<td>LoA, γ</td>
<td>3.84 (−2.43 to 10.11)</td>
<td></td>
</tr>
</tbody>
</table>

CI, confidence interval; CL, confidence limit; LoA, loss of ambulation; LS, least squares; NSAA, North Star Ambulatory Assessment; PODCI, Pediatric Outcomes Data Collection Instrument. 

Role of Corticosteroids in the DMD Treatment Landscape

- Corticosteroids remain the standard of care
- Data on prednisone vs deflazacort are emerging via post-hoc analysis
- FOR-DMD, a double-blind, randomized, prospective study on the comparison of prednisone vs deflazacort, is ongoing

Personal communication Basil Darras.
Considerations for the Comparison of Corticosteroids

- Access to the two corticosteroids was different in the USA before the approval of deflazacort
  - Post-hoc analysis also included international patients, with wider access to deflazacort
- Dosing and schedules vary between patients, posing a challenge when comparing different corticosteroids
Eteplirsen: Antisense Oligonucleotide

- Targets patients amenable to exon 51 skipping
- Additional data presented on respiratory function

Eteplirsen: Respiratory Function

- Patients in eteplirsen clinical trials (amenable to exon 51 skipping, on glucocorticoids) compared with natural history control

### Annual change in FVC % predicted (assessed between age 10 years and 18 years)

<table>
<thead>
<tr>
<th>Study</th>
<th>Natural history control (n = 20)</th>
<th>Eteplirsen-treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>201/202 (ambulatory)</td>
<td>−6.00%</td>
<td>−2.19% (n = 12)</td>
</tr>
<tr>
<td>204 (mainly non-ambulatory)</td>
<td>−6.00%</td>
<td>−3.66% (n = 20)</td>
</tr>
<tr>
<td>301 (ambulatory, interim analysis)</td>
<td>−6.00%</td>
<td>−3.79% (n = 46)</td>
</tr>
</tbody>
</table>

Golodirsen: Antisense Oligonucleotide

- Targets patients amenable to exon 53 skipping
- Interim analysis data were presented
  - Dystrophin production quantified in muscle biopsies of 25 patients treated with golodirsen

Results:
- Mean percent of normal dystrophin protein increased from 0.095% at baseline to 1.019% at Week 48
- Exon 53 skipping had increased significantly

Antisense Oligonucleotide Therapies

- Eteplirsen has been approved in the USA, with golodirsen still under investigation
- Patients amenable to skipping of exon 51 (etepirslen) and 53 (golodirsen) are candidates
- More efficacy data are required for golodirsen; clinical studies are ongoing
- Further eteplirsen studies are also ongoing

Personal communication Basil Darras.
Ataluren

- Ataluren has been approved by the EMA in Europe for ambulatory patients age ≥ 2 years with nonsense-mutation DMD
- **Label extension for patients ≥ 2 to < 5 years approved May 2018**
  - Safety profile was shown to be comparable in younger patients

Tian C et al. Presented at ICNMD; abstract number 807.
Ataluren in Patients Age ≥ 2 to < 5 Years

Study 030:
• Observational, phase 2 study to evaluate safety and pharmacokinetics in patients age ≥ 2 to < 5 years

Study goal:
• Assess ataluren therapy for dystrophin restoration at a younger age before substantive muscle loss

Safety results:
• The safety profile was similar to that in older patients
• The most common TEAEs were:
  • Pyrexia
  • Ear infection
  • Nasopharyngitis

TEAE, treatment-emergent adverse event.

Ataluren in Patients Age ≥ 2 to < 5 Years

Study 030 (n = 12): TFT at baseline and Week 28

<table>
<thead>
<tr>
<th>Time (seconds)</th>
<th>Baseline</th>
<th>Week 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to run/walk 10 m</td>
<td>6</td>
<td>5.7</td>
</tr>
<tr>
<td>Time to climb 4 stairs</td>
<td>5.7</td>
<td>3.4</td>
</tr>
<tr>
<td>Time to stand from a supine position</td>
<td>6.5</td>
<td>3.2</td>
</tr>
</tbody>
</table>

TFT change from baseline to Week 28

<table>
<thead>
<tr>
<th>Activity</th>
<th>CINRG natural history</th>
<th>Study 030</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to run/walk 10 m, seconds</td>
<td>n = 31</td>
<td>n = 12</td>
</tr>
<tr>
<td></td>
<td>−0.32</td>
<td>−0.6</td>
</tr>
<tr>
<td>Time to climb 4 stairs, seconds</td>
<td>n = 28</td>
<td>n = 12</td>
</tr>
<tr>
<td></td>
<td>−1.3</td>
<td>−2.1</td>
</tr>
<tr>
<td>Time to stand from a supine position, seconds</td>
<td>n = 25</td>
<td>n = 12</td>
</tr>
<tr>
<td></td>
<td>−0.65</td>
<td>−3.3</td>
</tr>
</tbody>
</table>

Ataluren in Patients Age ≥ 2 to < 5 Years

Study 030 (n = 12):
NSAA at baseline and Week 28

<table>
<thead>
<tr>
<th>Study 030 (n = 12): NSAA at baseline and Week 28</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study 030</td>
</tr>
<tr>
<td>Change from baseline to Week 28</td>
</tr>
<tr>
<td>CINRG natural history</td>
</tr>
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</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Change from baseline to Week 28</th>
<th>CINRG natural history</th>
<th>Study 030</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAA 8-item score n = 11</td>
<td>0.00</td>
<td>1.5</td>
</tr>
<tr>
<td>NSAA 3-item score n = 11</td>
<td>0.09</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Treatment of Younger Patients

• Initial trials focused on active motor decline phase (age 4–6 years)
• Studies are expanding into older, non-ambulatory, and younger patients
• Earlier treatment appears to be more efficacious
Considerations for Long-Term Treatment

• Studies to evaluate the long-term efficacy and safety of ataluren are ongoing
• Safety results are encouraging
• We need to understand the safety implications of long-term therapy
Micro-Dystrophin Gene Therapy

- Micro-dystrophin gene therapy is challenging due to gene size
- Micro-gene therapy targets key functional protein areas
  - Aims to create a semi-functional protein
  - Several studies under way in the USA
- Initial results are encouraging
- CRISPR-Cas9 for gene editing may have a role in the future

CRISPR, Clustered Regularly Interspaced Short Palindromic Repeats.
Key Messages

• There is now an approved treatment for SMA, 125 years after the first description of the disease by Werdnig and Hoffman

• Nusinersen is an effective and safe treatment for patients with SMA; results have been best in presymptomatic patients treated early

• Gene therapy with AVXS-101 and splicing modification with risdiplam seem promising, and may be approved in the future

• Steroids continue to be the standard of care in DMD

• Eteplirsen and ataluren have been approved in the USA and Europe, respectively, for the treatment of specific mutations; there are other treatments on the horizon
Therapeutic Update on Neuromuscular Disorders

SMA AND DMD

Conference Highlights From 2018