Diagnostic, Management and Treatment Strategies for DMD

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Neuromuscular Research Center
Duchenne is a X-linked Rare, Relentless and Fatal Disease of Boys and Young Men

<table>
<thead>
<tr>
<th>Muscle Biopsies</th>
<th>Newborn/Infant</th>
<th>3-7 years</th>
<th>7 years</th>
<th>Early Teens</th>
<th>Early 20s</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
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<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
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</table>

**Clinical Course**

- ![Image](image7.png)
- ![Image](image8.png)
- ![Image](image9.png)
- ![Image](image10.png)
- ![Image](image11.png)
- ![Image](image12.png)

*Progressive paralysis, respiratory failure, cardiomyopathy and premature death*
DMD pathomechanism

Gene abnormality at Xp21 loci

Absence of dystrophin

Structural defect

Membrane instability

Apoptosis / Necrosis

Gene abnormality at Xp21 loci

↓

Absence of dystrophin

Structural defect

Membrane instability

Apoptosis / Necrosis

Activation of NF-κB

Inflammation

Satellite Cell Activation

Muscle Fiber Regeneration

Fibrosis

Fiber Death

Adapted from Engvall & Wewer (2003) FASEB 17:1579
CK vs. Age
(3 to 17 years)

CK values may be 10-fold higher in younger patients with DMD
(e.g. 25,000 vs 2,500 in a 3 year old vs. 12 year old)
Six main categories for therapeutic targets for DMD

One addresses primary genetic defect; rest address downstream aspects of the pathogenesis

Targeting any single pathway may be an approvable mono-therapy

Future treatment paradigm may involve targeting multiple pathways to have greater patient impact
Glucocorticoids target NF-κB which is Chronically Activated in DMD

- miRNAs in muscle microenvironments cause variable dystrophin in muscular dystrophy
- miRNAs are elevated in dystrophic myofibers and increase with age and disease severity (use as a biomarker)
- Inflammatory cytokines induce miRNAs, and antiinflammatories block their expression
- miRNAs provide a precision medicine target in dystrophy
Potential for Combination Treatments in DMD

- Increasing muscle mass and regeneration
- Decreasing inflammation and fibrosis
- Correcting perturbations in Calcium handling
- Replacement of dystrophin/utrophin
- Correcting blood flow regulation
- Mitochondria dysfunction
- Decreasing inflammation and fibrosis

DMD Therapeutic Development

- NF-κB Is Chronically Activated in DMD
- Prednisone / Prednisolone
- Deflazacort (Emflaza, PTC)

Current Trials:
- Vamorolone (ReveraGen)
  - Dissociative steroids (decreased AEs)
- Edasalonexent (Catabasis)
  - covalently linked salicylic acid (ASA) and docosahexaenoic acid (DHA),
  - synergistically leverages the ability of both compounds to intracellularly inhibit activated NF-κB
Contemporary Treatments that have Affected the Natural History of Disease Progression and Survival in DMD

1. Glucocorticoids

2. Management of spine deformity
   - Glucocorticoids
   - Timely spine surgery for curves >30 to 40 degrees

3. Pulmonary management
   - Airway clearance strategies/mechanical cough assistance
   - Noninvasive ventilation

4. Cardiac management
   - Early afterload reduction (e.g., ACE inhibitors)
   - Recognition and management of heart failure
Duchenne is a X-linked Rare, Relentless and Fatal Disease of Boys and Young Men

Natural History of DMD

Prior to treatment 1960s
- 5 years: Loss of Standing
- 9 years: Loss of Ambulation
- 14 years: Loss of Self Feeding
- 20 years: Death

1970–1990 Spinal surgery and ventilation
- 5 years: Loss of Standing
- 9 years: Loss of Ambulation
- 14 years: Loss of Self Feeding
- 20 years: Ventilation

Contemporary: With steroids and improved cardiac management
- 5 years: Loss of Standing
- 9 years: Loss of Ambulation
- 14 years: Loss of Self Feeding
- 20 years: Ventilation

Steroids affect disease progression in DMD over the entire course of the disease prolonging clinically meaningful functions (time to loss of milestones)

Long-term effects of glucocorticoids on function, quality of life, and survival in patients with Duchenne muscular dystrophy: a prospective cohort study

Declining FVC%p Linked to Clinically Meaningful Thresholds and Risk of Death (Based on CINRG Data)

Median Absolute FVC (Liters) by Age and GC use in DMD


Peak in median FVC is shown and the point at which the median absolute FVC value drops below 1 l.
Age at Loss of Ambulation Predicts Age at Onset of 1 liter FVC (CINRG Data)

FVC < 1 liter increases risk of death

HR (95% CI) 4.1 (1.3, 13.1)

Ambulatory patients age 9-18 at study entry

McDonald et al. Lancet, 2018
Motor and Cognitive Assessment of Infants and Young Boys with Duchenne Muscular Dystrophy: Results from the Muscular Dystrophy Association DMD Clinical Research Network. Connolly et al. 
(n=25; 1.8±0.8 years)
Twenty-five steroid naive boys four to 30 months of age with genetically confirmed DMD were enrolled.

Treated boys gained an average of 0.5 points on the Bayley-III gross motor scaled score (GMSS) compared to the Historical Control Cohort who, on average, declined 1.3 points (p=0.03)

Connolly et al. submitted 2018
Advancements in RNA Therapy & Exon Skipping in DMD
Ataluren enables the ribosome to bypass a nonsense mutation and produces a functional protein

Ataluren causes the ribosome to bypass a premature stop codon

Allowing for the formation of a functional protein

- Orally bioavailable compound
- High specificity for nonsense readthrough without affecting normal termination codons
- Mechanism of action is distinct from exon-skipping drugs
Ataluren slows progression measured by 6MWT in subgroup where measure can be responsive in a 1-year trial

Phosphorodiamidate Morpholino Oligomer (PMO)

- Bind sequence-specifically to RNA targets\(^1\)
- Chemically modified nucleic acid analog\(^2\)
- Stable in serum and intracellularly\(^3\)
- Uncharged backbone\(^4\)

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Exon Skipping Proposed Mechanism of Action
e.g. Exon-51–Amenable DMD Patients

Normal Dystrophin mRNA

Exon 48-50 Deletion Disrupts Reading Frame

Unstable/No Dystrophin Protein: DMD

Target Outcome: Shortened Dystrophin Protein
Exon Skipping PMOs in late stage clinical development programs to address up to ~30% of all DMD Patients


Mutations not amenable to exon skipping, 20%
Other mutations amenable to exon skipping, 30%

Eteplirsen (FDA approved): PMO for skipping of Exon 51
Golodirsen; Viltolarsen: PMO for skipping of Exon 53
Casimersen: PMO for skipping of Exon 45
Eteplirsen Is a Phosphorodiamidate Morpholino Oligomer (PMO)

- Sequence length: 30 nucleotide bases
- Administered through weekly IV infusions of 30 mg/kg
- Doses studied (IV) 0.5 – 50 mg/kg
- Safety database of >150 patients
- >260 patients post-marketing
Dystrophin Increases and Correct Localization after Eteplirsen Treatment (Study 202 Week 180)

<table>
<thead>
<tr>
<th>Eteplirsen-Treated Week 180</th>
<th>Untreated Controls</th>
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<tbody>
<tr>
<td>01002</td>
<td>DMD #1</td>
</tr>
<tr>
<td>01007</td>
<td>DMD #5</td>
</tr>
<tr>
<td>01012</td>
<td>DMD #2</td>
</tr>
<tr>
<td>01003</td>
<td>DMD #6</td>
</tr>
<tr>
<td>01008</td>
<td>DMD #3</td>
</tr>
<tr>
<td>01013</td>
<td>01008</td>
</tr>
<tr>
<td>01004</td>
<td>0113</td>
</tr>
<tr>
<td>01009</td>
<td>0115</td>
</tr>
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</tbody>
</table>

*Patient 01005 declined the optional 4th surgical biopsy*
Increased Dystrophin Detected by All 3 Methods at Week 180 with Eteplirsen

<table>
<thead>
<tr>
<th>Method</th>
<th>Absolute Differences of Means (Treated vs Untreated Exon 51–Amenable Patient*) (% of Normal)</th>
<th>Fold Increase</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDPF</td>
<td>+16.27%</td>
<td>15.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intensity</td>
<td>+13.20%</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Western blot</td>
<td>+0.85%</td>
<td>11.6</td>
<td>0.007</td>
</tr>
</tbody>
</table>

*Untreated Control Group n=3 201/201 baseline + n=6 study 301 baseline
Clinically Meaningful Benefit Greater After 1 Year

DYSTROPHIN

% Normal Dystrophin

Eteplirsen Study 201/202 (N=11)
Eteplirsen Study 301 (N=12)

FVC%p

6MWT

6MWT (m)

Eteplirsen Study 201/202 (N=12)
Eteplirsen Study 301 (N=60)
Ambulatory EC (N=12)

LOA

Probability of Remaining Ambulatory (%)

Eteplirsen Study 201/202 (N=12)
Eteplirsen Study 301 (N=60)
Ambulatory External Control (N=12)
Golodirsen (Exon 53): Novel Dystrophin Production at Week 48 by Western blot (n=25)

Mean Baseline = 0.095% normal (SD 0.0680)
Mean On-treatment = 1.019% normal (SD 1.0328)

10.7-Fold Increase in Mean Dystrophin by Western Blot (Week 48)
<table>
<thead>
<tr>
<th>Method</th>
<th>Dose</th>
<th>Baseline Mean % (SD)</th>
<th>On-treatment Mean % (SD)</th>
<th>Fold Changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>% exon skipped molality (RT-PCR)</td>
<td>40 mg/kg</td>
<td>0.0 (0.0)</td>
<td>17.4 (7.2)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>80 mg/kg</td>
<td>0.0 (0.0)</td>
<td>43.9 (16.7)</td>
<td></td>
</tr>
<tr>
<td>% dystrophin (Western blot)*</td>
<td>40 mg/kg</td>
<td>0.3 (0.1)</td>
<td>5.7 (2.4)</td>
<td>19</td>
</tr>
<tr>
<td></td>
<td>80 mg/kg</td>
<td>0.6 (0.8)</td>
<td>5.9 (4.5)</td>
<td>9.8</td>
</tr>
</tbody>
</table>
Clinical changes with Exon 53 skipping (Viltolarsen)

**Stand from Supine (Velocity)**

**Climb 4-stairs (Velocity)**
Clinical changes with Exon 53 skipping (Viltolarsen)

**Run/walk 10 meters**

- Viltolarsen
- DNHS

**North Star Ambulatory Assessment**

- Viltolarsen
- DNHS

Change in Mean Velocity (m/sec)

Baseline 13weeks 25weeks

Change in Total Score

Baseline 13weeks 25weeks
Clinical Outcome Measures in DMD

• Function tests:
  – Northstar Ambulatory Assessment (NSAA)
  – 6 minute walk test
  – Manual and quantitative strength assessments
  – Pulmonary function testing (PFTs)
  – Performance of upper limb score (PUL)
  – Patient reported outcomes
• Currently, there are no reliable clinical ambulation endpoint outcome measurement tools for children ages 2 to 5 years old.
What are some limitations of prior studies (ie 6mw)?

- Interpretation of velocity based data as a measure of functional ability requires adjustment for age and stature.

- Why?
  - Velocity is a product of stride length and cadence
  - Stride length has not previously been normalized for height and age in many of our routine clinical outcome measures for community ambulation.
Problems with interpreting data from community based step monitoring:

• Stride length is the variable most altered in DMD
  – Higher predictor of clinical outcomes (especially in early disease)

• Step Cadence varies only slightly in DMD (until later stages of disease)
• How do we normalize stride length using anthropometric data?:
  • divide stride length by height to create a standardized stride to height ratio (SHR).
Stride:Height Ratio - A developmentally adjusted anthropometric standard

Stride length = Height(X) at different gaits / velocities in humans

<table>
<thead>
<tr>
<th>Gait</th>
<th>SHR</th>
<th>Stride Length</th>
</tr>
</thead>
<tbody>
<tr>
<td>Walking</td>
<td>0.8</td>
<td>14 inch</td>
</tr>
<tr>
<td>Speed Walking</td>
<td>1.2</td>
<td>15-17 inch</td>
</tr>
<tr>
<td>Running</td>
<td>1.5-1.9</td>
<td>18-20 inch</td>
</tr>
<tr>
<td>Sprinting</td>
<td>&gt;=2</td>
<td>21-24 inch</td>
</tr>
</tbody>
</table>
Stride:Height Ratio (SHR) in DMD

– Methods:
  • 24 boys with DMD (Dx Confirmed) and 36 typically-developing control boys

  • Ages of 4 to 12 Y.O

  • Participants assessed at baseline and at 1 year
Stride:Height Ratio (SHR) in DMD

– Methods Cont':

• Clinical assessments used:
  – Anthropometric measures
  – Six-minute walk test (6MWT)
  – Timed 10 and 25 meter walk/run tests
  – Stride length (m) = total distance (m) / # strides registered on calibrated StepWatch™ activity monitor.
  – Patient reported outcomes: PODC1
StepWatch®
Activity Monitor
In DMD shows
decreased function
SHR Trajectory declines with age in DMD relative to peers.

SHR at fastest pace:
- Controls: 1.08 +/- 0.12 with no change at one year
- DMD: 0.74 +/- 0.14, p<0.0001

*shortening of SHR with disease progression over one year: 0.08 +/- 0.11 (p<0.0081)
POSNA pediatric musculoskeletal functional health questionnaire
Clinical important because it trends with the patient’s report using a mobility based self report assessments
Use of Stride:Height as a clinical outcome tool

• Stride: height ratio (SHR) using step activity monitors can serve as a simple clinic or community-based to standardize ambulatory measures across ages in DMD for use in clinical trials.

• SHR is a gait parameter indicative of disease status and to determine responsiveness to newer therapies and record a longitudinal record as they age and progress through the disease course.

• Normalization of SHR in DMD may indicate benefits from treatments.

• May be a useful tool in all children with mobility impairments.
UC Davis Neuromuscular Medicine & Rehabilitation Research Center and CINRG Network