Clinical Trials in DMD: Role of qMR Imaging
Krista Vandenborne, PhD
Director, ImagingDMD Project
Hundreds of Duchenne community members gathered to #MakeDuchenneHistory at FDA Advisory Committee meeting - April 24, 2016
Validation of MR Biomarkers in DMD

- **Study 1: Ambulatory**
- **Study 2: Transition to non-ambulatory**

<table>
<thead>
<tr>
<th></th>
<th>DMD</th>
<th>Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>146</td>
<td>53</td>
</tr>
<tr>
<td>Age baseline 5-14yrs</td>
<td>8.0 ±3.3</td>
<td>8.8 ±2.4</td>
</tr>
<tr>
<td>6MWT</td>
<td>357.1 ±78</td>
<td>600.7 ±81</td>
</tr>
<tr>
<td>Current Age 5-18 yrs</td>
<td>11.7±2.6</td>
<td></td>
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<tr>
<td>Non-Ambulatory</td>
<td>31</td>
<td>-</td>
</tr>
</tbody>
</table>

- **CHOP** - Philadelphia, PA
- **OHSU/Shriner’s** – Portland, OR
- **UF** - Gainesville, FL
Quantitative Magnetic Resonance

- Noninvasive
- Objective
- Large sampling volume
- Muscle structure/Physiology

Imaging (MRI)

Spectroscopy (MRS)
$T_1$ weighted MR Image

Control

Duchenne

Thigh muscles
Fat Fraction increases at all ages

A

**Vastus Lateralis**

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>Control</th>
<th>DMD Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-6</td>
<td><img src="image1" alt="Control" /></td>
<td><img src="image2" alt="DMD Baseline" /></td>
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<tr>
<td>7-8</td>
<td><img src="image1" alt="Control" /></td>
<td><img src="image2" alt="DMD Baseline" /></td>
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<tr>
<td>9-10</td>
<td><img src="image1" alt="Control" /></td>
<td><img src="image2" alt="DMD Baseline" /></td>
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<tr>
<td>11-12</td>
<td><img src="image1" alt="Control" /></td>
<td><img src="image2" alt="DMD Baseline" /></td>
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C

**Soleus**

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<td>11-12</td>
<td><img src="image1" alt="Control" /></td>
<td><img src="image2" alt="DMD Baseline" /></td>
</tr>
</tbody>
</table>
Fat Fraction increases at all ages
Sensitivity: 1 year change in DMD

MRS - Spectroscopy

<table>
<thead>
<tr>
<th></th>
<th>DMD BL</th>
<th>DMD 12 months</th>
<th>P (change over 1 year)</th>
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<tbody>
<tr>
<td>VL FF</td>
<td>0.18 ± 0.17</td>
<td>0.25 ± 0.19</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SOL FF</td>
<td>0.10 ± 0.07</td>
<td>0.12 ± 0.10</td>
<td>&lt;0.0001</td>
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</table>

MRI T$_2$ (ms)

<table>
<thead>
<tr>
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<th>DMD BL</th>
<th>DMD 12 months</th>
<th>P (change over 1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFLH</td>
<td>50.4 ± 11.4</td>
<td>56.0 ± 13.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>VL</td>
<td>48.6 ± 10.4</td>
<td>53.0 ± 11.9</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GRA</td>
<td>39.3 ± 4.9</td>
<td>40.5 ± 6.6</td>
<td>NS</td>
</tr>
<tr>
<td>MG</td>
<td>42.1 ± 6.4</td>
<td>45.2 ± 8.0</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PER</td>
<td>42.5 ± 7</td>
<td>44.5 ± 6.4</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>SOL</td>
<td>42.2 ± 5.5</td>
<td>44.1 ± 8.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TA</td>
<td>37.5 ± 4.6</td>
<td>38.6 ± 5.2</td>
<td>&lt;0.0001</td>
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<tr>
<td>TP</td>
<td>36.5 ± 2.4</td>
<td>37.3 ± 2.9</td>
<td>0.0004</td>
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</tbody>
</table>

Vastus Lateralis Fat Fraction with Age

Progression Model for Vastus Lateralis Fat Fraction

Age (yr)

MRS Fat Fraction VL

0.00 0.25 0.50 0.75

4 8 12 16
Do MR measures show disease progression in subjects when the 6min walk does not?

Source: parentprojectmd.org

Correlation between MR measures and Functional measures
Correlation between qMR and Clinical Measures of Function

Timed tests

- 10m walk/run
- Stair climbing
- Get up from supine
- 6 min walk
Correlation Coefficients

- Treat each time point as a separate observation (n=421)
- Stronger correlations in upper leg

<table>
<thead>
<tr>
<th></th>
<th>VL FF</th>
<th>SOL FF</th>
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<tbody>
<tr>
<td>Supine to stand</td>
<td>0.77</td>
<td>0.64</td>
</tr>
<tr>
<td>10m walk/run</td>
<td>0.75</td>
<td>0.65</td>
</tr>
<tr>
<td>4 Stairs</td>
<td>0.73</td>
<td>0.66</td>
</tr>
<tr>
<td>6MWT</td>
<td>-0.63</td>
<td>-0.57</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th></th>
<th>BFLH T₂</th>
<th>VL T₂</th>
<th>GRA T₂</th>
<th>PER T₂</th>
<th>MG T₂</th>
<th>SOL T₂</th>
<th>TA T₂</th>
<th>TP T₂</th>
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<tbody>
<tr>
<td>Supine to stand</td>
<td>0.75</td>
<td>0.76</td>
<td>0.26</td>
<td>0.72</td>
<td>0.57</td>
<td>0.65</td>
<td>0.61</td>
<td>0.54</td>
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<td>P=.044</td>
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<tr>
<td>10m walk/run</td>
<td>0.66</td>
<td>0.76</td>
<td>0.38</td>
<td>0.72</td>
<td>0.64</td>
<td>0.65</td>
<td>0.64</td>
<td>0.6</td>
</tr>
<tr>
<td>4 stairs</td>
<td>0.68</td>
<td>0.73</td>
<td>0.35</td>
<td>0.73</td>
<td>0.65</td>
<td>0.68</td>
<td>0.65</td>
<td>0.6</td>
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<tr>
<td>6MWT</td>
<td>-0.55</td>
<td>-0.64</td>
<td>-0.21</td>
<td>-0.57</td>
<td>-0.54</td>
<td>-0.55</td>
<td>-0.57</td>
<td>-0.53</td>
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<tr>
<td>P&gt;.05</td>
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P<.0001 unless otherwise specified
Can MRI Detect the Effect of Corticosteroids?

Examination of effects of corticosteroids on skeletal muscles of boys with DMD using MRI and MRS

ABSTRACT

Objective: To evaluate the effects of corticosteroids on the lower extremity muscles in boys with Duchenne muscular dystrophy (DMD) using MRI and magnetic resonance spectroscopy (MRS).

Methods: Transverse relaxation time (T2) and fat fraction were measured by MR/MRS in lower extremity muscles of 15 boys with DMD (age 5.0–8.9 years) taking corticosteroids and 15 corticosteroid-naive boys. Subsequently, fat fraction was measured in a subset of these boys at 1 year. Finally, MR/MRS data were collected from 10 corticosteroid-naive boys with DMD (age 5–8.9 years) at baseline, 3 months, and 6 months. Five boys were treated with corticosteroids after baseline and the remaining 11 served as corticosteroid-naive controls.

Results: Cross-sectional comparisons demonstrated lower muscle T2 and less intramuscular (IM) fat infiltration in boys with DMD on corticosteroids, suggesting reduced inflammation/damage and fat infiltration with treatment. Boys on corticosteroids demonstrated less increase in IM fat infiltration at 1 year. Finally, T2 by MR/MRS detected effects of corticosteroids on leg muscles as early as 3 months after drug initiation.

Conclusions: These results demonstrate the ability of MR/MRS to detect therapeutic effects of corticosteroids in reducing inflammatory processes in skeletal muscles of boys with DMD. Our work highlights the potential of MR/MRS as a biomarker in evaluating therapeutic interventions in DMD. Neurology® 2014;83:974–980

GLOSSARY

6MWT = 6-minute walk test; CHOP = Children’s Hospital of Philadelphia; DMD = Duchenne muscular dystrophy; Dpa = dystrophin; GRF = gastrocnemius; MG = medial gastrocnemius; MRS = magnetic resonance spectroscopy; OHSU = Oregon Health & Science University; Par = parasternal; Sal = soleus; STEAM = stimulated echo acquisition mode; TA = tibialis anterior; TP = tibialis posterior; TE = echo time; TR = repetition time; UF = University of Florida; VL = vastus lateralis.

Duchenne muscular dystrophy (DMD) is a devastating form of muscular dystrophy caused by the absence of dystrophin, making muscle cell membranes fragile and susceptible to mechanical damage.1,2 Currently, there is no cure for the disease. Corticosteroids have been reported to slow disease progression in DMD.3,4 However, the mechanism by which corticosteroids preserve muscle function in DMD is not fully understood.

Among several proposed mechanisms, corticosteroids are thought to reduce inflammation in dystrophic muscle.1,4,5 MRI, in particular T2-weighted MRI, is sensitive to alterations in muscle chemistry and structure induced by processes like damage/inflammation and fat infiltration.1,6,7
Corticosteroid Dose (n=6)

- Age at initiation: 6.7 ± 1.3 years
- 5 Deflazacort: dose 0.82-0.9 mg/kg/day
- 1 Prednisone: 0.75 mg/kg/day
3 month change in $T_2$ MRI

Arpan I et al. Neurology. 2014; PMID: 25098537

Change in MRI $T_2$ in 3 months

- MG
- Per
- Sol
- TA
- TP

Corticosteroid
Corticosteroid-naïve

$p=0.06$
6 month change in $T_2$ MRI

Change in MRI $T_2$ in 6 months

- MG
- Per
- Sol
- TA
- TP

Corticosteroid
Corticosteroid-naïve

* * *

Arpan I et al. Neurology. 2014; PMID: 25098537
Clinical Trials....

• Implementation in clinical trials in ambulatory patients

  > Eli Lilly – Tadalafil – Substudy - COMPLETED
  > Sarepta 4658-203 – Exon skipping - Exploratory
  > Catabasis Therapeutics – anti-inflammatory – Primary
  > Summit Therapeutics – Utrophin modulation – Primary
MR Biomarkers in the Upper Extremity

• >2/3 of patients DMD non-ambulatory
• Facilitate inclusion in clinical trials
• Sensitive in ambulatory and non-ambulatory

Need transitional outcome measures - sensitive across wide range of disease stages

MR of functionally important upper extremity muscles
Upper Arm

CON

DMD – 13 yrs
- non-ambulatory -

BB

TB
Shoulder

DMD – 13 yrs
- non-ambulatory -
Fat Fraction in UE Muscles across ages

Fat Fraction in UE Muscles across ages

Age Group (years)

Fat Fraction

Biceps

Deltoid
T$_2$ MRI in upper limb muscles

N=37 subjects (15 non-ambulatory)
Age 12.1 ± 3.0 years
Correlation between UE qMR Biomarkers and Function

<table>
<thead>
<tr>
<th></th>
<th>PUL total</th>
<th>PUL high</th>
<th>PUL middle</th>
<th>PUL distal</th>
<th>max grip</th>
<th>max key</th>
</tr>
</thead>
<tbody>
<tr>
<td>BB MRI-T2</td>
<td>-0.91</td>
<td>-0.60</td>
<td>-0.71</td>
<td>-0.81</td>
<td>0.61</td>
<td>0.10</td>
</tr>
<tr>
<td>TB MRI-T2</td>
<td>-0.83</td>
<td>-0.64</td>
<td>-0.56</td>
<td>-0.63</td>
<td>0.75</td>
<td>0.13</td>
</tr>
<tr>
<td>Dixon BB FF</td>
<td>-0.83</td>
<td>-0.47</td>
<td>-0.75</td>
<td>-0.74</td>
<td>0.48</td>
<td>0.14</td>
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<tr>
<td>Dixon TB FF</td>
<td>-0.77</td>
<td>-0.56</td>
<td>-0.47</td>
<td>-0.60</td>
<td>0.47</td>
<td>0.16</td>
</tr>
</tbody>
</table>

PUL, Grip Strength, Key pinch
Summary

• Lower Extremity qMR measures are sensitive to disease progression, correlate with function, and sensitive to corticosteroid treatment – Moving into clinical trials.

• Upper extremity qMRI can successfully be implemented in upper arm and shoulder muscles to develop sensitive biomarkers – potential for clinical trials in non-ambulatory patients
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University of Florida
- Glenn Walter
- Lee Sweeney
- Sean Forbes
- Bill Triplett
- Claudia Senesac
- Rebecca Willcocks
- Donavon Lott
- Barry Byrne

OHSU
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- Barry Russman
- Erica Finanger

CHOP
- Gihan Tennekoon
- Ann Tokay Harrington

Other
- Richard Finkel
- Michael Daniels

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