New (and Old) Corticosteroid news

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January 25, 2017
Disclosure

• Advisory Boards
  – Sarepta, Ionis, Roche, Genzyme, AveXis

• Data Management Safety Board
  – Catabasis

• Site PI
  – Sarepta, Biogen, Roche, Avexis, Italafarmaco,
  – NS Pharma
Why (Not) Corticosteroids?

…or “How do I (not) love thee, let me count the ways”…

- Weight gain
- Cushingoid features
- Insulin resistance/diabetes
- Behavior
- Osteopenia, fractures
- Delayed puberty
- Hirsutism
- Growth stunting
- Cataracts
- Adrenal insufficiency/risk for adrenal crisis
Corticosteroids; early years

1974- Pilot (Drachman, Toyka, Myer-Lancet)
– 1980-91’s: ClDD Group
– Daily prednisone (0.75mg/kg/day) improves strength
Twice Weekly high dose oral prednisone
(search for alternative)

• Background
  – From 1991-1999 I succeeded in getting virtually every boy's family to TRY daily corticosteroids (0.75mg/kg/day)
  – Side effects: obesity, linear growth slowing/arrest such that more than 50% would discontinue therapy

• Methods
  – 10mg/kg/ week- prednisone in two daily doses
  – Exam, height, weight, quantitative strength with hand held manometer

• 20 consecutive treated boys with DMD
- Twice weekly corticosteroids were effective in Pilot study of boys with DMD (age 8 +/-1.2 years) over one year.
  - P=.001 for upper extremity
  - p=.002 for grip
  - p=<.0001 for lower extremity
- Linear growth was maintained
- Obesity rates were the same as untreated historical controls.
- Cushingnoid features including hirsutism, acne, stria, and hypertension did not occur. No cataracts developed.
- 16 treated >1 year; 15/16 remained stronger than baseline
- 2002: Connolly, Schierbecker, Renne, Florence, Neuromuscular disorders
2(b) Lower Extremity

- 2002: Connolly, Schierbecker, Renne, Florence, Neuromuscular disorders
mdx Mouse: Twice weekly oral prednisolone improves strength and survival

Grip Strength

Survival

2007: Muscle and Nerve: Keeling Golumbek, Streif, and Connolly
Randomized, blinded trial of twice weekly vs. daily prednisone in Boys with DMD

- **64 boys**
  - 4 to 10 yrs; daily (0.75mg/kg) vs weekend (10mg/kg over 2 days) TX for 12 months

**RESULTS**: Equally effective for Quantitative muscle testing and MMT (arm and leg) and timed functional testing over 12 months

- FVC improved 2.8% weekend, 0.6% in Daily
- Behavior **IMPROVED** equally in both groups
- DEXA -lumbar bone density improved in weekend treated cohort, decreased in daily

CDC: STRONG STATEMENT

- 2010: GLUCOCORTICOIDs-only medication available that
  - slows the decline in muscle strength and function
  - reduces risk of scoliosis
  - stabilizes pulmonary function
  - Improves Cardiac function

CDC
Corticosteroid Recommendations

- Prednisone 0.75 mg/kg/day
- Deflazacort 0.9 mg/kg/day
- Alternatives
  - 1) weekend 10mg/kg/week
  - 2) 0.75 mg=1.2 mg/kg every other day
  - 3) 0.75mg/kg/day first 10 days of month

- WU standard of care is twice weekly steroids
Clinical course: Weekend Steroids

TJ and weekend prednisone

Strength in Pounds

- Quadriceps
- Biceps

Age (Years)

2003 2012
Steroids are not a cure

• 2010? Who is treating “Everyone?”
• Who is staying on treatment?
• How about after ambulation is lost?
Non-Ambulatory boys/men

N=91 (Collaborating sites: Washington University, Nationwide Children’s, UCDavis, Minnesota, Boston)

47 on No Corticosteroids
25 on Daily Corticosteroids
19 on twice Weekly corticosteroids.

Reliable outcomes (ICC >.95) included Vital Capacity, Brooke Scale, Grip strength and Pinch and Key strength.
Corticosteroids benefit non-ambulatory boys and Men

<table>
<thead>
<tr>
<th>Corticosteroid Use</th>
<th>FVC % Predicted</th>
<th>Age (Yrs)</th>
<th>Brooke Scale</th>
<th>EK Scale</th>
<th>Grip, Right (Newt)</th>
<th>Grip Left (Newt)</th>
<th>Key Right (Newt)</th>
<th>Key Left (Newt)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily n = 25</td>
<td>51 ± 25</td>
<td>16.5 ± 4.5</td>
<td>3.2 ± 1.4*</td>
<td>13.1 ± 4.2</td>
<td>38 ± 23*</td>
<td>34 ± 27</td>
<td>16 ± 11*</td>
<td>16 ± 12*</td>
</tr>
<tr>
<td>2x week n = 19</td>
<td>57 ± 3.4</td>
<td>15.2 ± 3.4</td>
<td>3.1 ± 1.0*</td>
<td>13.1 ± 3.8</td>
<td>31 ± 18</td>
<td>28 ± 18</td>
<td>13 ± 7</td>
<td>12 ± 7</td>
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<tr>
<td>None n = 47</td>
<td>40 ± 19</td>
<td>17.5 ± 4.7</td>
<td>4.4 ± 1.1</td>
<td>15.7 ± 5.8</td>
<td>19 ± 17</td>
<td>19 ± 17</td>
<td>8 ± 7</td>
<td>7 ± 6</td>
</tr>
</tbody>
</table>

Brooke Scale FVC and hand function better on Corticosteroids: 2014, Connolly et al Muscle and Nerve
Deflazacort

Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy

ABSTRACT

Objective: To assess safety and efficacy of deflazacort (DFZ) and prednisone (PRED) vs placebo in Duchenne muscular dystrophy (DMD).

Methods: This phase III, double-blind, randomized, placebo-controlled, multicenter study evaluated muscle strength among 196 boys aged 5-15 years with DMD during a 52-week period. In phase 1, participants were randomly assigned to receive treatment with DFZ 0.9 mg/kg/d, DFZ 1.2 mg/kg/d, PRED 0.75 mg/kg/d, or placebo for 12 weeks. In phase 2, placebo participants were randomly assigned to 1 of the 3 active treatment groups. Participants originally assigned to an active treatment continued that treatment for an additional 40 weeks. The primary efficacy endpoint was average change in muscle strength from baseline to week 12 compared with placebo. The study was completed in 1995.

Results: All treatment groups (DFZ 0.9 mg/kg/d, DFZ 1.2 mg/kg/d, and PRED 0.75 mg/kg/d) demonstrated significant improvement in muscle strength compared with placebo at 12 weeks. Participants taking PRED had significantly more weight gain than placebo or both doses of DFZ at 12 weeks; at 52 weeks, participants taking PRED had significantly more weight gain than both DFZ doses. The most frequent adverse events in all 3 active treatment arms were Cushingoid appearance, erythema, hirsutism, increased weight, headache, and nasopharyngitis.

Conclusions: After 12 weeks of treatment, PRED and both doses of DFZ improved muscle strength compared with placebo. Deflazacort was associated with less weight gain than PRED.

Classification of evidence: This study provides Class I evidence that for boys with DMD, daily use of either DFZ and PRED is effective in preserving muscle strength over a 12-week period.

Neurology® 2016;87:2123-2131
### Table 1: Demographic and baseline characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Deflazacort 0.9 mg/kg/d (n = 51)</th>
<th>Deflazacort 1.2 mg/kg/d (n = 49)</th>
<th>Prednisone 0.75 mg/kg/d (n = 46)</th>
<th>Placebo (n = 50)</th>
<th>Total (n = 196)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, y</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>8.8 (2.5)</td>
<td>8.8 (3.0)</td>
<td>8.8 (2.9)</td>
<td>8.5 (3.1)</td>
<td>8.8 (2.9)</td>
</tr>
<tr>
<td>Median</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Min, max</td>
<td>5, 15</td>
<td>5, 15</td>
<td>5, 15</td>
<td>5, 15</td>
<td>5, 15</td>
</tr>
<tr>
<td><strong>Male, n (%)</strong></td>
<td>51 (100)</td>
<td>49 (100)</td>
<td>46 (100)</td>
<td>50 (100)</td>
<td>196 (100)</td>
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<tr>
<td><strong>Race, n (%)</strong></td>
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<td></td>
<td></td>
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<tr>
<td>White</td>
<td>46 (90.2)</td>
<td>45 (91.8)</td>
<td>45 (97.8)</td>
<td>49 (98)</td>
<td>185 (94.4)</td>
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<tr>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (0.5)</td>
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<tr>
<td>Other</td>
<td>5 (9.8)</td>
<td>3 (6.1)</td>
<td>1 (2.2)</td>
<td>1 (2.0)</td>
<td>10 (5.1)</td>
</tr>
<tr>
<td><strong>Height, cm</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>131 (17)</td>
<td>130 (20)</td>
<td>131 (18)</td>
<td>130 (18)</td>
<td>131 (18)</td>
</tr>
<tr>
<td>Median</td>
<td>128.5</td>
<td>127</td>
<td>127.9</td>
<td>123.1</td>
<td>127.7</td>
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<tr>
<td>Min, max</td>
<td>101.6, 180.0</td>
<td>97.0, 169.6</td>
<td>106.7, 170.0</td>
<td>101.3, 174.0</td>
<td>97.0, 180.0</td>
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<td><strong>Weight, kg</strong></td>
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<td>Mean (SD)</td>
<td>31 (13)</td>
<td>29 (11)</td>
<td>32 (15)</td>
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<td>30 (14)</td>
</tr>
<tr>
<td>Median</td>
<td>26.4</td>
<td>25.5</td>
<td>25.4</td>
<td>23.2</td>
<td>24.7</td>
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<tr>
<td>Min, max</td>
<td>17.1, 73</td>
<td>16.3, 69.5</td>
<td>15.5, 84</td>
<td>14.8, 95</td>
<td>14.8, 95</td>
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<tr>
<td><strong>Body mass index, kg/m^2</strong></td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>17.1 (3.9)</td>
<td>16.7 (3.0)</td>
<td>17.7 (4.2)</td>
<td>17.2 (3.6)</td>
<td>17.2 (3.7)</td>
</tr>
<tr>
<td>Median</td>
<td>16.2</td>
<td>16.7</td>
<td>16.2</td>
<td>15.9</td>
<td>16.2</td>
</tr>
<tr>
<td>Min, max</td>
<td>9.8, 28.9</td>
<td>9.6, 25.5</td>
<td>12.1, 31.2</td>
<td>12.7, 31.4</td>
<td>9.6, 31.4</td>
</tr>
</tbody>
</table>
Deflazacort (effective and less weight gain than daily corticosteroid treatment)

STRENGTH

FDA Approval Feb 2017
Why do corticosteroids work?

1) Immune suppression? Not via B or T cells (mdx RAG2 mice still develop weakness AND still respond to twice weekly steroids) (Golumbek PT, Keeling RM, Connolly AM. Strength and corticosteroid responsiveness of mdx mice is unchanged by RAG2 gene knockout. Neuromuscul Disord. 2007)

2) “Intermittent Glucocorticoid steroid dosing enhances repair without eliciting muscle atrophy” Quattrocelli, Barfield, Warner, Vo, Hadhazy, Early, Domonbreun and McNally JCI 2017

1) Pulse Steroids (prednisone or deflazacort) result in SMALLER injury after fiber damage from lazer
Why do corticosteroids work?

- Repair is improved by daily or weekly corticosteroids

- Quattrocelli, Barfield, Warner, Vo, Hadhazy, Early, Domonbreun and McNally  JCI 2017
Dream slide: DMD and BMD Diagnosis At Birth
(as part of Newborn screening)

Mutation Specific Therapy

Mutation Non-Specific Therapy

Early intervention for Cognitive Impairment

Increase walking to age 30-60; lifespan normal
Infants and young boys with DMD have Gross motor function is measurable and abnormal compared to peers. (p<.0001)

Infants and young boys with DMD show decline in motor function (Bayley-3) on average in the first years of life.

Infant outcomes using Bayley-III N=24 (Collaborating sites: Washington University, Nationwide Children's, UCDavis, Minnesota, Boston, Newcastle)
Many thanks to
Washington University: Julaine Florence, Catherine Siener, Becca Gadeken, Craig Zaidman, Paul Golumbek, MaryMike Cradock, Pallavi Anand, Jeanine Schierbecker, JP Miller
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Newcastle: Kate Bushby, Michelle Eagle
Nemours Hospital: Rich Finkel
UT Southwestern: Susan Iannaconne

The boys and men with DMD, their families and MDA (US)