New (and Old) Corticosteroid news

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New (and Old) Corticosteroid news

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• Disclosures
  • Advisory Boards
    – Sarepta, Ionis, Roche, Genzyme, AveXis
  • Data Management Safety Board
    – Catabasis
  • Site PI
    – Sarepta, Biogen, Roche, Avexis, Italafarmaco,
    – NS Pharma

Anne M. Connolly, MD
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DMD: Progression over 8 years

2 years

5 years

10 years
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.
- Cushingoid 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
• **2002:** Connolly, Schier becker, Renne, Florence, Neuromuscular disorders
**mdx Mouse:** Twice weekly oral prednisolone improves strength and 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

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

2013—Prolongs life

"All-cause Mortality and Cardiovascular outcomes with prophylactic steroid therapy in DMD" Schram et al, Am J of Am Coll Cardiol, 2013
CDC (2010) 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

Washington University standard of care is twice weekly steroids
NB:
Twice weekly
And 10 days on/off not in chart

Adrenal insufficiency
- Educate on signs, symptoms, and management of adrenal crisis
- Prescribe intramuscular hydrocortisone for administration at home
  - 50 mg for children aged <2 years old
  - 100 mg for children aged ≥2 years old and adults
- Stress dosing for patients taking >12 mg/m² per day of prednisone/deflazacort daily
  - Might be required in the case of severe illness, major trauma, or surgery
  - Administer hydrocortisone at 50–100 mg/m² per day

Do not stop steroids abruptly
- Implement PJ Nicholoff steroid-tapering protocol
- Decrease dose by 20–25% every 2 weeks
- Once physiological dose is achieved (3 mg/m² per day of prednisone or deflazacort) switch to hydrocortisone 12 mg/m² per day divided into three equal doses
- Continue to wean dose by 20–25% every week until dose of 2.5 mg hydrocortisone every other day is achieved
- After 2 weeks of dosing every other day, discontinue hydrocortisone
- Periodically check morning CRH-stimulated or ACTH-stimulated cortisol concentration until HPA axis is normal
- Continue stress dosing until HPA axis has recovered (might take 12 months or longer)
Clinical course: Twice weekly Steroids

TJ and weekend prednisone

Strength in Pounds

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 ± 20*</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>
</tr>
<tr>
<td>None n=47</td>
<td>40 ± 19±4.7</td>
<td>17.5±5.8</td>
<td>4.4 ± 1.1</td>
<td>15.7 ± 17</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
Efficacy and safety of deflazacort vs prednisone and placebo for Duchenne muscular dystrophy

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Darcy L. Fehlings, MD
Alan Pestronk, MD
Jerry R. Mendell, MD
Richard T. Moxley III, MD
Wendy King, PT
John T. Kissel, MD
Valerie Cwik, MD
Michel Vanasse
Julaine M. Florence, DPT
Shree Pandya, DPT
Jordan S. Dubow, MD
James M. Meyer, PharmD

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>Age, y</td>
<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>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>9</td>
<td>8</td>
<td>8</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>Min, max</td>
<td>5, 15</td>
<td>5, 15</td>
<td>5, 15</td>
<td>5, 15</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>51 (100)</td>
<td>49 (100)</td>
<td>46 (100)</td>
<td>50 (100)</td>
<td>196 (100)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>White</td>
<td>46 (90.2)</td>
<td>45 (91.8)</td>
<td>45 (97.8)</td>
<td>49 (98)</td>
</tr>
<tr>
<td></td>
<td>Asian</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td></td>
<td>Other</td>
<td>5 (9.8)</td>
<td>3 (6.1)</td>
<td>1 (2.2)</td>
<td>1 (2.0)</td>
</tr>
<tr>
<td>Height, cm</td>
<td>Mean (SD)</td>
<td>131 (17)</td>
<td>130 (20)</td>
<td>131 (18)</td>
<td>130 (18)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>128.5</td>
<td>127</td>
<td>127.9</td>
<td>123.1</td>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td>Weight, kg</td>
<td>Mean (SD)</td>
<td>31 (13)</td>
<td>29 (11)</td>
<td>32 (15)</td>
<td>31 (15)</td>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>26.4</td>
<td>25.5</td>
<td>25.4</td>
<td>23.2</td>
</tr>
<tr>
<td></td>
<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>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<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>
</tr>
<tr>
<td></td>
<td>Median</td>
<td>16.2</td>
<td>16.7</td>
<td>16.2</td>
<td>15.9</td>
</tr>
<tr>
<td></td>
<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>
</tr>
</tbody>
</table>
Deflazacort (effective and less weight gain than daily corticosteroid treatment)

FDA Approval Feb 2017

STRENGTH

Weight
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

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

• Repair is improved by daily or weekly corticosteroids

• Atrophy develops only in mdx treated daily

• Quattrocelli, Barfield, Warner, Vo, Hadhazy, Early, Domonbreun and McNally JCI 2017
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, UC Davis, Minnesota, Boston, Newcastle)

2013: Neuromuscular Disorders: Connolly, Florence, Cradock, et al
2013: Neuromuscular Disorder: Pane et al
Twice weekly corticosteroids and heart function

Objective: Look at LV function before and after 3 months of high dose twice weekly corticosteroids
25 with MD, 17 with DMD, 3 with BMD
LV function improved in three month prospective study (10mg/kg over two days) p=0.009 for FS%

<table>
<thead>
<tr>
<th></th>
<th>Before Steroids, Mean (SD)</th>
<th>After Steroids, Mean (SD)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CK, U/L</td>
<td>13,589.6 (14,099.7)</td>
<td>7631 (5587.6)</td>
<td>0.047*</td>
</tr>
<tr>
<td>LVEDD, mm</td>
<td>35.52 (6.8)</td>
<td>33 (6.2)</td>
<td>0.001†</td>
</tr>
<tr>
<td>LVESd, mm</td>
<td>23.12 (6.13)</td>
<td>23.4 (5)</td>
<td>0.722</td>
</tr>
<tr>
<td>FS%</td>
<td>32 (8.6)</td>
<td>36.8 (6.8)</td>
<td>0.009†</td>
</tr>
</tbody>
</table>

Nearly all clinical trials limited to Ambulatory and “cooperative”

Two problems
1) Some trials (e.g., rare exons won’t be possible using only the 25%
2) Some therapies may work better earlier…or later

MDA-DMD Center grant-develop outcomes
Clinical Trial complete:  Does twice weekly corticosteroids improve Bayley 3 Gross Motor function in children less than 30 months? Short answer yes, paper in Review in Neurology

Infants with DMD have Gross motor function is abnormal compared to peers.
2013: Neuromuscular Disorders: Connolly, Florence, Cradock, et al
2013: Neuromuscular Disorder : Pane et al

In young boys with DMD Bayley-3 Gross motor function declines on average in the first years of life: 2014: Pediatric Neurology 2014 Connolly, Florence Cradock et al

Clinical Trial complete:  Does twice weekly corticosteroids improve Bayley 3 Gross Motor function in children less than 30 months? Short answer yes, paper in Review in Neurology
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
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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UCDavis: Craig McDonald, Erica Goude, Linda Johnson, Alina Nicorici, Erik Henricson
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Boston Children’s: Basil Darras, Peter Kang, Sue Riley, Elizabeth Shriber, R Parad
Newcastle: Kate Bushby, Michelle Eagle
Nemours Hospital: Rich Finkel
UT Southwestern: Susan Iannaconne

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