Deflazacort Clinical Policy

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Overview

- Duchenne Muscular Dystrophy Background and Epidemiology
- Evidence on Safety and Efficacy of Deflazacort
- Clinical Policy
Duchenne Muscular Dystrophy
Background and Epidemiology
Duchenne Muscular Dystrophy (DMD)

• Duchenne muscular dystrophy (DMD) is an X-linked genetic disease affecting the dystrophin gene.

• Dystrophin is a protein that interfaces between the plasma cell membrane of muscle fibers and extracellular matrix\(^1\).
  
  – Dystrophin is necessary for normal muscle function, protecting the glycoprotein complex at the membrane.

  – Loss of dystrophin results in degeneration of muscle fibers, resulting in muscle weakness, the primary symptom of DMD.

From UpToDate\(^1\). The dystrophin associated protein complex. Courtesy of Dr. K. O’Brien and Dr. L. Kunkel, Children's Hospital, Boston, MA.
Duchenne Muscular Dystrophy (DMD)

- DMD typically manifests as muscle weakness in males at 2 to 3 years of age¹. Diagnosis of DMD often occurs around age 5².
  - Genetic tests or muscle biopsy are required to confirm diagnosis of DMD compared to other dystrophinopathies (such as Becker muscular dystrophy [BMD])¹,².

- Muscle weakness begins in the distal limb muscles, resulting in difficulty running, jumping, and even walking¹.
  - About 82% of patients with DMD are restricted to wheelchairs between 10 through 14 years of age².

- Cardiomyopathy, caused by fibrosis of the left ventricular wall, can lead to heart failure and arrhythmias in the patient’s teenage years¹. Other significant medical complications from DMD are respiratory, bone fractures, and mental health.

- The most common cause of death is acute respiratory failure (due to scoliosis and progressive muscle weakness)¹. The majority of deaths occur in the 20s.
DMD Epidemiology

- A population-based survey in 4 US states estimates the prevalence of DMD and BMD to be 1 in 7,250 males ages 5 to 24\(^2\). It was estimated that, out of 2.37 million males ages 5 to 24 in 4 US states, there were 349 with DMD or BMD\(^3\).

  - Other prevalence studies conducted in the US, Canada, Northern England, and Wales found similar population estimates\(^1\).

- DMD has higher prevalence among Hispanics and non-Hispanic whites than among non-Hispanic blacks\(^2\).

- The prevalence of DMD in Washington Medicaid FFS is estimated to be 100. The incidence of new DMD cases by birth is estimated to be 6.
DMD Standard of Care

• Glucocorticoids can help improve motor function, pulmonary function, and reducing the risk of scoliosis in patients with DMD\(^1\).
  
  – Treatment with steroids typically begins around 7 years of age\(^2\).
  
  – Approximately 57% to 69% of patients with DMD and BMD are treated with steroids\(^2\). Prednisone is the most commonly used steroid (between 64% to 78%)\(^2\).

• Cardiac, pulmonary, orthopedic, mental health, nutritional, growth, weight, and pain conditions are all commonly associated with DMD as well\(^1\).
Evidence on Safety and Efficacy of Deflazacort
Deflazacort vs. prednisone

• Deflazacort was studied against prednisone for the treatment of DMD in 4 randomized control trials
  – All four studies were rated by GRADE system to have very low quality of evidence on outcomes of muscle strength, motor outcomes, weight gain, and cataracts.
  – The quality of evidence for comparative effectiveness outcomes were downgraded due to risk of bias, imprecision, and lack of applicability

• There is no comparative evidence for deflazacort and prednisone beyond 2 years of use for DMD.
Deflazacort vs. prednisone

- Reitter (1995); Dubowitz (2000) published the results of a trial of deflazacort vs. prednisone in boys with DMD or BMD from 1995.
  - N = 100; study duration = 2 years
  - No statistically significant difference in muscle strength (Medical Research Council scale score) or motor outcomes
  - Prednisone group had more weight gain (no data) while deflazacort group developed more cataracts (36% vs. 3%), and 20% of enrollees did not complete the study (14 discontinued due to weight gain)

- Reitter (1995) published interim results from 67 boys in 1995 and only presented graphical data without reporting data by intervention group. Dubowitz (2000) presented the results of 100 boys at a conference workshop.
Deflazacort vs. prednisone

• Brooke (1996); Griggs (2016) published the results of a trial of deflazacort vs. prednisone in boys with DMD or BMD from 1995.
  
  – N = 167; study duration = 3 months (primary) and 1 year (other outcomes)
  
  – Both deflazacort and prednisone were significantly more effective than placebo for both muscle strength and motor outcomes. No difference between active groups at 12 weeks or at 1 year.
  
  – Prednisone group had statistically significant weight gain at 1 year (mean difference of 5.05 kg vs 8.45 kg) while deflazacort group developed more cataracts (6.6% vs 4.4%).

• Results of the study were originally presented at the 75th American Academy of Neurology meeting (1996) but were published as part of the FDA clinical review (2016).
Deflazacort vs. prednisone

• Bonifati (2000) published the results of a trial of deflazacort vs. prednisone in boys with DMD from 2000.
  
  – N = 18; study duration = 2 years
  
  – No statistically significant difference in muscle strength (Medical Research Council scale score) or motor outcomes (results were presented only graphically)
  
  – Prednisone group had more weight gain (mean difference from baseline: 8.7 kg vs. 4.6 kg) while deflazacort group developed more cataracts.

• No significant differences were found at 3, 6, or 9 months but found statistically significant improvement at 12 months with prednisone (the authors suggest that this is due to more severe patients dropping out of the study).
Deflazacort vs. prednisone

- Karimzadeh (2012) published the results of a trial of deflazacort vs. prednisone in boys with DMD from 2012.
  - N = 34; study duration = 18 months
  - Deflazacort had a statistically significant difference in motor outcomes at 12 months but had no statistically significant difference at 18 months. Muscle strength was not evaluated.
  - Prednisone group had more weight gain at 12 months and 18 months.

- Study had significant loss to follow-up (17.6% deflazacort; 29.4% prednisone) and did not use intent-to-treat analysis. Authors did not report on randomization, blinding, or baseline characteristics.
Systematic Reviews

• Three systematic reviews reviewed the evidence of deflazacort vs. prednisone for the treatment of DMD.
  – Each systematic review had different inclusion criteria and no systematic review included all 4 trials from the previous section.

• Two systematic reviews concluded that deflazacort and prednisone were similarly effective in muscle strength and motor outcomes and that deflazacort leads to less weight gain

• The third systematic review did not find enough evidence to make a conclusion on the effectiveness of motor outcomes and found very low quality evidence (high risk of bias) of prednisone causing more weight gain
The AAN Practice Guidelines on Corticosteroid Treatment of DMD was a good methodological quality guideline.

- The only RCT included for this section was Bonifati et al., 2000

The guidelines do not recommend one corticosteroid over the other and cited a low confidence in the quality of the comparative evidence.

Guidelines provide “B” level evidence [moderate value of benefit relative to risk and moderate confidence in evidence] for prednisone to improve strength and improve pulmonary function. All other outcomes for both prednisone and deflazacort are “C” level evidence [small value of benefit relative to risk and low confidence of evidence].
Emflaza price?

• In February 2017, Marathon Pharmaceuticals announced a list price of Emflaza (deflazacort) to cost approximately $89,000 per patient per year. On March 16, PTC Therapeutics announced the purchase of Marathon Pharmaceuticals for $140 million. The new pricing for Emflaza has not been announced.

  – AWP for a single tablet was $294.00. New AWP has not been announced.

  – Deflazacort is administered as 0.9 mg/kg/day. The maximum tablet strength is 36 mg, so for patients above 88 lbs., deflazacort would require multiple tablets and increasing the cost even more.

• Deflazacort was available from pharmacies in the United Kingdom for approximately $1000 per year.

• Prednisone is available at a MAC of $0.05 per 20 mg tablet. This translates to an approximate cost of $55 per patient per year.
Conclusions

• Based on a review of the randomized clinical trials, systematic reviews and treatment guidelines:
  – there is very low quality evidence that there is no difference in efficacy between deflazacort and prednisone
  – there is very low quality evidence that prednisone is associated with more weight gain than deflazacort but clinical significance has not been studied

• Prednisone is the lower cost alternative based on current pricing information
Deflazacort Clinical Policy
For approval (initial and renewal):

<table>
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<tr>
<th>Criteria</th>
<th>Rationale</th>
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<tr>
<td>Prednisone will be the preferred corticosteroid for the treatment of DMD</td>
<td>Prednisone is the lower cost, equally effective alternative</td>
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<td>Deflazacort will be reviewed on a case–by–case basis to determine medical necessity for the treatment of DMD</td>
<td>Very low quality of evidence on efficacy and safety.</td>
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<td>Deflazacort will not be approved for off–label indications</td>
<td>Deflazacort for use in other disease states has not been evaluated by the FDA</td>
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Questions?

Motion: “I move the Medicaid Fee-For-Service Program implement the limitations for deflazacort on slide 19 as recommended.”

Motion: Figueroa

2nd: Brown

Passed