Duchenne muscular dystrophy quantification of muscular parameters and prednisone therapy
Beenakker, Ernesto Alexander Christiaan

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Steroid therapy in Duchenne muscular dystrophy: a review of the literature.
Steroid therapy in Duchenne muscular dystrophy: a review of the literature.

Submitted

Abstract

Duchenne muscular dystrophy (DMD) is a neuromuscular disorder characterised by progressive muscle weakness with loss of ambulation at age 9,5. Despite the discovery of the genetic defect causal therapy is not yet available. Many drug trials have been conducted to prolong ambulation in DMD patients but only steroids do have a beneficial effect on muscle force and muscle function.

It still remains controversial however, whether patients should be treated with steroids, since treatment is associated with a number of severe side effects. Dose reduction and the use of intermittent schedules could not prevent these side effects without losing the positive effect on muscle force and muscle function. Although prednisone preserves muscle force and muscle function on the short term, its long-term benefit and long-term side-effects are largely unknown. Also the effects of prednisone on the quality of life of ambulant DMD patients is unknown. Therefore, one should be reserved with intermittent prednisone administration.
Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive neuromuscular disorder characterised by progressive weakness of the limb girdle musculature. The mean age at diagnosis is around 4.5 years.\(^1\) Due to progressive muscle weakness patients become wheelchair bound at a mean age of 9.5 years.\(^2\) The mean age at death for ventilated DMD patients is 25.3 years.\(^3\)

In 1987, the gene that encodes the protein dystrophin was cloned.\(^4\) Dystrophin, which is absent in DMD patients,\(^5\) is part of the cytoskeleton and is associated with the sarcolemma.\(^6\) Despite the discovery of this underlying defect, there is no causal therapy.

Many different drugs have been tried to slow down disease progression.\(^7\)–\(^{14}\) Only for steroids a short-term beneficial effect on muscle force and muscle function has been shown. However, steroids are not yet universally used in DMD since it firstly remains unclear if the presence of short-term side effects such as weight gain and cushingoid appearance outweigh their benefits and secondly the long-term beneficial effects on disease course and possible side effects of steroids are unknown. The purpose of this study was to review steroid trials that have been conducted in DMD and to determine whether the beneficial effects of steroids outweigh their side effects.

Methods

A search for trials in DMD was carried out in Clinical Evidence (BMJ Publishers), metaregister RCTs (Biomed Central), Cochrane Library, Embase from 1974 to 2004 and a ‘second opinion search’ in Medline from 1966 to 2004. The keywords used were: (controlled) clinical trial, randomised controlled trial, meta-analysis, multicentre-study, deflazacort, oxandrolon*, prednison*, prednisolon* and Duchenne muscular dystrophy.

Twenty-three articles, which reported the effects of the steroids mentioned above were analysed. Three of 23 articles were not used for further analysis because these articles could not be translated in a universal language.\(^{15}\)–\(^{17}\) However, some data could be extracted from the abstracts.
Table 1.
Steroid trials in DMD. ? = unknown; deflazacort (def.); prednisone (pred.); wheel chair bound (wcb); randomised controlled trial (RCT)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Author</th>
<th>Study design</th>
<th>Dosage</th>
<th>Number of Patients</th>
<th>Age range</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxandrolone</td>
<td>2001</td>
<td>(19)</td>
<td>RCT</td>
<td>0,1 mg/kg/d</td>
<td>50</td>
<td>5 – 10 year</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>1997</td>
<td>(17)</td>
<td>open pilot</td>
<td>0,1 mg/kg/d</td>
<td>10</td>
<td>6 – 9 year</td>
<td>3 months</td>
</tr>
<tr>
<td>Deflazacort</td>
<td>2001</td>
<td>(19)</td>
<td>open retrospective</td>
<td>0,9 mg/kg/d</td>
<td>30</td>
<td>7 – 15 year</td>
<td>&gt; 5 year</td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>(19)</td>
<td>double blind</td>
<td>0,9 mg/kg/d (def.)</td>
<td>18</td>
<td>5,2 – 14,6 year</td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0,75 mg/kg/d (pred.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>(19)</td>
<td>double blind</td>
<td>0,9 mg/kg/d (def.)</td>
<td>67</td>
<td>5 – wcb year</td>
<td>2 year</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0,75 mg/kg/d (pred.)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1994</td>
<td>(17)</td>
<td>RCT</td>
<td>2,0 mg/kg alternate-day</td>
<td>28</td>
<td>?</td>
<td>2 year</td>
</tr>
<tr>
<td></td>
<td>1991</td>
<td>(11)</td>
<td>double blind controlled</td>
<td>1,0 mg/kg/d</td>
<td>28</td>
<td>5 – 11 year</td>
<td>9 months</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>2002</td>
<td>(29)</td>
<td>open</td>
<td>0,75 mg/kg/d for 10 days on,off</td>
<td>4</td>
<td>under 5 years of age</td>
<td>30 - 90 months</td>
</tr>
<tr>
<td></td>
<td>2001</td>
<td>(19)</td>
<td>double blind</td>
<td>0,75 mg/kg/d (pred.)</td>
<td>10</td>
<td>?</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>1999</td>
<td>(17)</td>
<td>RCT</td>
<td>0,5 mg/kg/d</td>
<td>?</td>
<td>?</td>
<td>1 year</td>
</tr>
<tr>
<td></td>
<td>1996</td>
<td>(19)</td>
<td>?</td>
<td>1,0 mg/kg alternate day</td>
<td>10</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>(19)</td>
<td>RCT cross-over</td>
<td>0,35 mg/kg/d</td>
<td>37</td>
<td>4 – 19,4 year</td>
<td>6 months</td>
</tr>
<tr>
<td></td>
<td>1993</td>
<td>(22)</td>
<td>open</td>
<td>0,75 mg/kg first 10 days of each month</td>
<td>32</td>
<td>6 – 14 year</td>
<td>1,5 year</td>
</tr>
<tr>
<td></td>
<td>1974</td>
<td>(19)</td>
<td>double blind</td>
<td>5 mg/kg alternate-day</td>
<td>7 pairs</td>
<td>6 – 9 year</td>
<td>3 year</td>
</tr>
<tr>
<td>Prednisone</td>
<td>2003</td>
<td>(27)</td>
<td>open pilot prospective</td>
<td>0,75 mg/kg/d daily for 2 weeks then 1,25 mg/kg alternate days control group</td>
<td>5</td>
<td>2 – 4 year</td>
<td>47 – 63 months</td>
</tr>
<tr>
<td>Year</td>
<td>(?)</td>
<td>Study Type</td>
<td>Drug</td>
<td>Dosage</td>
<td>Number</td>
<td>Age Range</td>
<td>Follow-up</td>
</tr>
<tr>
<td>------</td>
<td>-----</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------------------------</td>
<td>--------</td>
<td>----------------</td>
<td>-----------</td>
</tr>
<tr>
<td>2002</td>
<td>(21)</td>
<td>open</td>
<td>Oxandrolone</td>
<td>0.1 mg/kg/d</td>
<td>50</td>
<td>5 – 10 year</td>
<td>6 months</td>
</tr>
<tr>
<td>1997</td>
<td>(22)</td>
<td>open pilot</td>
<td>Deflazacort</td>
<td>0.9 mg/kg/d</td>
<td>10</td>
<td>6 – 9 year</td>
<td>3 months</td>
</tr>
<tr>
<td>1995</td>
<td>(23)</td>
<td>open</td>
<td>Prednisolone</td>
<td>0.75 mg/kg/d for 10 days, off</td>
<td>4</td>
<td>under 5 years of age</td>
<td>30 - 90 months</td>
</tr>
<tr>
<td>1987</td>
<td>(24)</td>
<td>open</td>
<td>Prednisone</td>
<td>1.5 mg/kg/d</td>
<td>33</td>
<td>5 - 15 year</td>
<td>6 months</td>
</tr>
<tr>
<td>1974</td>
<td>(25)</td>
<td>open</td>
<td>Prednisone</td>
<td>2 mg/kg/d after 2-3 months</td>
<td>14</td>
<td>3.5 – 10.5 year</td>
<td>3 – 28 months</td>
</tr>
</tbody>
</table>
**Prednisone therapy**

*Non randomised controlled trials*

One of the first steroid trials in DMD was conducted in 1974 by Siegel et al.\(^{18}\) (Table 1). In this double-blind study, 7 pairs of clinically matched DMD patients were included. Prednisolone (5 mg/kg/d) was given to one patient of each matched pair, the other patient was given placebo. They reported a transient and non-specific benefit in only a few cases (Table 3).

In that same year Drachman et al.\(^{19}\) suggested that prednisone (2 mg/kg/d) might have a place in the treatment of DMD patients, since 13 of 14 patients showed an “improvement” of muscle strength and muscle function which lasted for 3 to 28 months. However, “all patients showed cushingoid changes in facial features within 2-4 weeks” (Table 2).

In 33 DMD patients aged 5-15 years, in which prednisone (1,5 mg/kg/d) was given for 6 months, a significant improvement in average muscle strength (subjective, modified Medical Research Council-scale, MRC 1-10), timed tests and functional grade was found.\(^{20}\) In individual patients average muscle strength, timed tests and functional grade were indicated as “better” in 21 of 33 (64%), 20 of 33 (61%) and 9 of 33 (27%), respectively. These variables did not change or worsen in the remaining patients. However, 6 of 33 (18%) patients dropped out because of weight gain, which was present in all patients and ranged from 5 to 45% of initial weight. Behavioural changes such as increased appetite, hyperactivity, insomnia and mood changes were reported in 12 of 33 (36%) patients.

To reduce the extent of side effects intermittent schedules were introduced. Fenichel et al.\(^{21}\) compared daily and alternate-day prednisone therapy in 98 DMD patients aged 5-15 years and reported that “alternate-day prednisone therapy effectively increases strength but does not sustain the improvement to the same extent as daily therapy or mitigate side-effects.” However, this study was an extension of their randomised, double blind, 6 months trial previously reported. Since DMD is a progressive disease, the reduction of muscle strength, which was noted on the alternate-day schedule, might be due to the natural progression of the disease instead of the dose schedule modification. On the other hand the extent of side-effects was not reduced during the alternate-day period which also might be due to the fact that the majority of patients already had been treated with prednisone for 12 months.

In an other intermittent schedule prednisolone (0,75 mg/kg/d) was given during the first 10 days of each month.\(^{22}\) This pilot study enrolled 32 DMD patients aged 6-14 years in whom muscle force (MRC) and muscle function were assessed. Mean muscle force was nearly unchanged for 6 months but it subsequently declined at 12 and 18 months. The change in muscle function showed a similar trend over the 18-month period. After 1 year, 20 of 27 (74%) of the patients had gained more than 10% of their
initial body weight. More recently, Connolly et al.\textsuperscript{23} reported the effects of twice weekly used prednisone (5 mg/kg/dose) in 20 DMD patients aged 5,2-10,7 years, in an open trial. Although all treated patients showed improvement of lower extremity strength, timed functional tests had only improved significantly in the younger patients (5-7 years) and side effects such as increased appetite and irritability were seen. DeSilva et al.\textsuperscript{24} suggested that prednisone might have a long-term beneficial effect since ambulation was prolonged by approximately 2 years in prednisone treated DMD patients compared to none treated ones. Despite dose reduction after 2-3 months from the initial daily dosage of 2 mg/kg/d to 2/3 of the original dose on an alternate day schedule, all patients developed cushingoid appearance and 12 of 16 (75%) developed increased appetite and excessive weight gain. A significant slowing of disease progression for at least 3 years in daily treated DMD patients (prednisone 0,75 mg/kg/d) compared with natural history controls was reported by Fenichel et al.\textsuperscript{25} However, these patients already completed two 6-month prednisone trials\textsuperscript{21} without a washout-period which might have affected this long-term beneficial effect.\textsuperscript{26} Merlini et al.\textsuperscript{27} also suggested a long-term beneficial effect of prednisone since prednisone treated patients were still able to arise from the floor at a mean age of 8,3 years after 55 months of treatment on average. However, in this open pilot study the prednisone group comprised only 5 DMD patients. Besides there was no beneficial effect on other timed tests (6 standardised stairs and running 10 m) despite a significant increase in leg muscle force. A functional improvement (Hammersmith motor ability score and walking 28 feet) was also reported by Kinali et al.\textsuperscript{28} Unfortunately this study comprised 4 patients of whom only 2 were followed for a longer period (6 years and 7,5 years).

Randomised controlled trials

Mendell et al.\textsuperscript{26} compared two prednisone dosages of 0,75 mg/kg/d and 1,5 mg/kg/d in a 6 months randomised controlled trial in which 103 DMD patients aged 5-15 years were included. In both prednisone groups muscle strength (modified MRC 1-10) improved. The increase in muscle strength was already noted at 1 month, continued at 2 and 3 months and remained stable until 6 months. Timed function tests also improved significantly. The extent of side-effects was similar in both prednisone groups. Initial body-weight increased 20% more in approximately 33% of the prednisone treated patients. Cushingoid appearance was present in 55% (0,75 mg/kg/d) and in 73% (1,5 mg/kg/d). Despite the improvement in muscle force and muscle function, prednisone was not recommended because the long-term benefits and side effects of prednisone

85
### Table 2.
Side effect evaluation and reported side effects in steroid trials.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Year</th>
<th>Author</th>
<th>Side effect evaluation</th>
<th>Intervals</th>
<th>Evaluated parameters</th>
<th>Reported side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxandrolone</td>
<td>2001</td>
<td>(33)</td>
<td>- blood analysis</td>
<td>0,6 month</td>
<td>Na, K, Cl, CO2, blood urea, nitrogen, creatinine, glucose, CK, cholesterol, HDL, LDL, liver function tests</td>
<td>15 adverse events in oxandrolone group; not specified, not significant</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- questioning parents and patients</td>
<td>0,1,3,6 month</td>
<td>none</td>
<td>increased appetite, aggressive behaviour, testicular size</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- clinical examination</td>
<td>0,1,3,6 month</td>
<td>height, weight, BP, eye examination</td>
<td>weight gain, cataracts, growth suppression</td>
</tr>
<tr>
<td></td>
<td>1997</td>
<td>(32)</td>
<td>- questioning parents</td>
<td>0,1,3 month</td>
<td>blood glucose, CBC, Ca, P, bilirubin, CK, glucose, Ca</td>
<td>cUSHINGOID appearance, increase appetite, weight gain, behavioural changes, GI symptoms, hirsutism, cataracts</td>
</tr>
<tr>
<td>Deflazacort</td>
<td>2001</td>
<td>(36)</td>
<td>- clinical examination</td>
<td>every 4 to 6 month</td>
<td>CK, glucose, electrolytes, Ht, CBC</td>
<td>cUSHINGOID appearance, increase appetite, weight gain, behavioural changes, GI symptoms, hirsutism, cataracts</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- blood analysis</td>
<td>every 8 month</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- urine analysis</td>
<td>every 4 month</td>
<td>height, weight, BP, eye examination</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- 24-h urine analysis</td>
<td>every 8 month</td>
<td>blood glucose, CBC, Ca, P, bilirubin, CK, glucose, Ca</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- questioning parents</td>
<td>every 4 to 6 month</td>
<td>CK, glucose, electrolytes, Ht, CBC</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2000</td>
<td>(36)</td>
<td>- questioning parents</td>
<td>start every 3 month</td>
<td>none</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- blood analysis</td>
<td>start, every 3 month</td>
<td>behavioural changes, insomnia, anorexia, increased appetite, gastrointestinal problems</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- clinical examination</td>
<td>start, every 3 month</td>
<td>CK, glucose, electrolytes, Ht, CBC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- X-ray left hand</td>
<td>start, every 3 month</td>
<td>cUSHINGOID appearance, acne, hirsutism, height, weight, BP</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- eye examination</td>
<td>start, 1 year</td>
<td>weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>(34)</td>
<td>- clinical controls</td>
<td>3, 6 month</td>
<td>- bone mineralization</td>
<td>weight gain</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- densitometry</td>
<td></td>
<td>- CK, alkaline phosphatase</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- biochemical markers</td>
<td></td>
<td>weight, height, BP</td>
<td>behavioural changes, increased appetite, cUSHINGOID appearance, hirsutism</td>
</tr>
<tr>
<td></td>
<td>1994</td>
<td>(35)</td>
<td>- clinical examination</td>
<td>every 2 month</td>
<td>WBC, RBC, Ht, glucose, CK, ions</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- X-ray chest, left hand</td>
<td>start, 24 month</td>
<td>weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- blood analysis</td>
<td>every 2 month</td>
<td>- bone age</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- eye examination</td>
<td>start, 2 year</td>
<td>- CBC, glucose, Ca, P, CK, Na, K, Cl</td>
<td>behavioural changes, increased appetite, cUSHINGOID appearance, hirsutism, acne, insomnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ECG</td>
<td>start, 24 month</td>
<td>weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1991</td>
<td>(36)</td>
<td>- laboratory</td>
<td>0,1,2,3,6,9,12 month</td>
<td>cUSHINGOID appearance, skin, behavioural changes, hirsutism, insomnia, gastrointestinal symptoms, appetite, cataracts, elevated glucose</td>
<td>behaviour, appetite, gastrointestinal, cUSHINGOID, hirsutism, acne, insomnia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- clinical evaluation</td>
<td>0,1,2,3,6,9,12 month</td>
<td>weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- ECG</td>
<td>every 3 month</td>
<td>- WBC, RBC, Ht, glucose, CK, ions</td>
<td></td>
</tr>
<tr>
<td>Prednisolone</td>
<td>2002</td>
<td>(37)</td>
<td>- clinical examination</td>
<td>unknown</td>
<td>weight gain</td>
<td>no prednisolone related side effects</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- bone density</td>
<td>1-6 years after prednisolone was started</td>
<td>weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1995</td>
<td>(38)</td>
<td>- blood analysis</td>
<td>0,3,6 month</td>
<td>blood count, Na, K, glucose, CK</td>
<td>weight gain (in non ambulant DMD patients), hirsutism, irritability, rounder cheeks, acne, alert, tired, increased self-confidence, weight loss, uneasiness</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>- questioning parents</td>
<td>after 6 month</td>
<td>weight gain</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1993</td>
<td>(39)</td>
<td>- eye examination</td>
<td>3,6,12,18 month</td>
<td>fundoscopy</td>
<td>weight gain, behavioural changes, acne</td>
</tr>
</tbody>
</table>
- questioning parents
- urine analysis
- clinical examination
- BP
- every 3 month
- not specified
- not mentioned
- questioning parents
- laboratory evaluation
- chest X-ray
- Prednisone
- at first 0,1,3,6 month followed by every 6 months
- weight, height, pulse, BP, fatigue, hunger, gastrointestinal problems, behavioural changes
- CBC, CK, CK-MB, aldolase, glucose, Ca, P, Ig G, A and M, hepatorenal and adrenal cortical functions
- questioning parents
- clinical examination
- laboratory evaluation
- cardiacologist
- opthalmologist
- X-ray
- bone mineral density
- bone maturation
- laboratory evaluation
- DEXA-scans
- at least once
- after 2 years (in only 2 boys)
- weight, height, pulse, BP, BT, cataracts, ankle oedema, cosmetic, behavioural changes
- glucose
- questioning parents
- laboratory evaluation
- clinical examination
- urine analysis
- questioning parents
- laboratory evaluation
- clinical examination
- urine analysis
- questioning parents
- laboratory evaluation
- clinical examination
- urine analysis
- questioning parents
- clinical examination
- laboratory evaluation
- clinical examination
- urine analysis
- questioning parents
- not mentioned
- about possible side-effects
- blood chemistry, CK, CBC
Table 3.
Number of dropouts, effect of steroids on muscle force and muscle function and general conclusion in conducted steroid trials in DMD, significant (sig.).

<table>
<thead>
<tr>
<th>Drug</th>
<th>Author</th>
<th>Drop-outs</th>
<th>Muscle force</th>
<th>Timed tests</th>
<th>Conclusion of authors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxandrolone</td>
<td>(33)</td>
<td>1 (disease progression, parents seeking alternative medicine)</td>
<td>QMT sig.</td>
<td>not sig.</td>
<td>oxandrolone may be useful since it is safe, accelerates linear growth, may have some beneficial effect in slowing progress of weakness</td>
</tr>
<tr>
<td></td>
<td>(32)</td>
<td>none</td>
<td>sig. improvement in muscle force (MRC 1-10)</td>
<td>not mentioned</td>
<td>results of pilot are sufficiently robust to conduct a double-blind controlled trial</td>
</tr>
<tr>
<td>Deflazacort</td>
<td>(31)</td>
<td>none</td>
<td>pulmonary function sig. increased</td>
<td>sig. walk longer, climb stairs, getting up from the floor at older age</td>
<td>no conclusion about the use of deflazacort</td>
</tr>
<tr>
<td></td>
<td>(35)</td>
<td>1 (loss of independent ambulation)</td>
<td>no sig. differences for muscle force between deflazacort and prednisone group</td>
<td>no sig. differences in functional score between deflazacort and prednisone group</td>
<td>no conclusion whether deflazacort or prednisone should be used</td>
</tr>
<tr>
<td></td>
<td>(34)</td>
<td>4 (weight gain)</td>
<td>muscle strength tends to improve (MRC)</td>
<td>slight shortening of time needed for rising from a supine position and stability in ability to stand up from a chair, mounting 4 steps and running 30 feet</td>
<td>prednisone and deflazacort improve the course of DMD</td>
</tr>
<tr>
<td></td>
<td>(37)</td>
<td>1 (appendectomy), 3 (Achilles tenotomy) 2 (cushingoid)</td>
<td>MRC index sig. increased</td>
<td>sig. improvement in climbing stairs, rising from a chair, Gower's sign and running</td>
<td>no definite statement is made</td>
</tr>
<tr>
<td></td>
<td>(30)</td>
<td>not mentioned</td>
<td>muscle force sig. improved (hand-held myometry)</td>
<td>Gower's manoeuvre sig. improved, no sig. difference for running 10 m between deflazacort and placebo</td>
<td>steroids could possibly be considered as a standard therapy in DMD if considerable slowing of the disease can be achieved with few side-effects. However more research and long-term follow-up are needed</td>
</tr>
<tr>
<td>Prednisolone</td>
<td>(28)</td>
<td>none</td>
<td>no improvement</td>
<td>walking 28 feet improved</td>
<td>prednisolone induced and maintained an improvement in muscle function. However, due to the small number of cases no advice can be given concerning prednisolone usage.</td>
</tr>
<tr>
<td></td>
<td>(26)</td>
<td>not mentioned</td>
<td>sig. improvement of muscle force in walking DMD patients</td>
<td>4 stairs and running 10 m improved significantly</td>
<td>prednisolone should at least be discussed and considered, especially in patients that are still walking</td>
</tr>
<tr>
<td>Reference</td>
<td>Dose</td>
<td>Effect</td>
<td>Side Effects</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------</td>
<td>------</td>
<td>--------</td>
<td>--------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td>19 (not specified)</td>
<td>improved after 6 month but decreased after 12 and 18 months</td>
<td>not mentioned</td>
<td>definite influence on muscle power at 3 and 6 months. However, further studies of the intermittent schedule versus daily dosage are needed to determine the effect on muscle function and the extent of side effects</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>none</td>
<td>no sig. improvement</td>
<td>no sig. improvement</td>
<td>although prednisolone may prove of transient and non-specific benefit in a few cases of this disease, it has no ultimate therapeutic value</td>
<td></td>
</tr>
<tr>
<td>Prednisone</td>
<td>(2)</td>
<td>none</td>
<td>no sig. improvement for individual muscles, only for leg megascoring</td>
<td>no sig. improvement in 6 stairs and 10m. effect on arise form the floor unclear</td>
<td>long-term steroid treatment is effective in prolonging function</td>
</tr>
<tr>
<td>(2)</td>
<td>4 boys stopped; 3 resumed after unknown period</td>
<td>sig. increase in upper and lower extremity strength</td>
<td>4 stairs, running 30 ft, rising from supine improved significantly only in boys aged 5-7 yr</td>
<td>prednisone significantly improves muscle strength and timed functional testing; the latter only in younger boys. However, the side effect of irritability must be considered and a larger trial with longer follow-up is needed to validate the beneficial effects</td>
<td></td>
</tr>
<tr>
<td>(2)</td>
<td>10 (4 due to side-effects, usually weight gain. Other 6 not mentioned)</td>
<td>was maintained for up to 3 years (MRC)</td>
<td>sig. improvement</td>
<td>prednisone significantly slows disease progression for at least 3 yr however benefits must be weighed against expected side effects</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>2 (side effects not specified)</td>
<td>improved in alternate-day but was not maintained at 6 months (MRC)</td>
<td>improved in alternate-day but was not maintained at 6 months</td>
<td>no suggestion</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>4 (without reason)</td>
<td>sig. increase in muscle strength (MRC)</td>
<td>sig. increased</td>
<td>prednisone 0.75 mg/kg/d is recommended for DMD patient who experience functional decline</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>1 DMD hyperactive and irritable behaviour, 1 DMD unblinded medication (placebo group) 2 needed surgery (prednisone group)</td>
<td>sig. improvement (MRC)</td>
<td>sig. improvement</td>
<td>despite the increase in muscle force and function prednisone is not yet advocated since the long-term benefit as well as the threshold dose for improvement remain to be determined</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>6 unacceptable weight gain</td>
<td>sig. improvement (MRC)</td>
<td>sig. improvement</td>
<td>prednisone was associated with an improvement in strength and function however further studies are needed to determine the long-term effects of prednisone</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>none</td>
<td>not evaluated</td>
<td>not evaluated</td>
<td>steroid therapy can provide long-term benefit. However benefits must outweigh side-effects</td>
<td></td>
</tr>
<tr>
<td>(9)</td>
<td>6 (1gastritis, 1hyperactivity, 1no apparent benefit, 3 side-effects outweigh the benefits not specified)</td>
<td>improved (not calculated statistically; MRC)</td>
<td>improved (not calculated statistically)</td>
<td>results suggest that prednisone provides a temporary, palliative treatment for some DMD patients</td>
<td></td>
</tr>
</tbody>
</table>
were unclear. Additionally, the threshold dose for improvement still had to be deter-
dined since side effects were already present in the lowest dose group.
This threshold dose was tried to be determined in a randomised controlled trial in
which daily prednisone 0.3 mg/kg/d or 0.75 mg/kg/d was administered for 6 months to
99 DMD patients aged 5-15 years. Muscle strength improved after 10 days in both
groups. In the high dose group the improvement reached a maximum at 3 months
and stayed until 6 months. At 3 months, however, the patients in the high dose group
were significantly stronger than those in the low dose group, indicating a dose related
response. Multiple side-effects such as weight gain, cushingoid appearance and
excessive hair growth were seen at 6 months in the group on 0.75 mg/kg/d, whereas,
in the group on 0.3 mg/kg/d only weight gain was seen. It was suggested that the
optimal dose is probably around 0.75 mg/kg/d despite the presence of side effects.
Bäckman and Henriksson\textsuperscript{30} conducted a 12 month randomised, double-blind cross
over trial in which prednisolone (0.35 mg/kg/d) was administered for 6 months to
37 DMD patients aged 4-19,4 years (22 ambulant and 15 non-ambulant). Muscle
force was only significantly increased in 3 of 24 muscle groups (dorsal ankle flexors
at the non-dominant side, knee flexors at the dominant side, and neck extensors) in
ambulant DMD patients. In non-ambulant DMD patients no significant changes in
muscle force were seen, neither in the prednisolone nor in the placebo period. To
what extent functional tests improved remains unclear.
Significant weight gain was only seen in non-walking DMD patients. They indirectly
suggested, in contrast with Griggs et al.,\textsuperscript{29} that the threshold dose for improvement is
around 0.35 mg/kg/d.
Since side effects seem to be inevitably associated with prednisone therapy it is
important to know to what extent daily life of patients is affected. However, this has
not yet been the subject of investigation.

\textbf{Other steroids}

To reduce side effects without impairing the beneficial effect of prednisone, dosages
were reduced, intermittent schedules introduced and other steroids such as deflazacort
and oxandrolone were tested.
Mesa et al.\textsuperscript{31} conducted a double-blind controlled trial with deflazacort in 28 DMD
patients aged 5-11 years. Muscle strength and timed function tests improved signi-
ficantly in the treated group. Side-effects after 9 months of treatment included mild
cushingoid appearance in 28\%, increased appetite in 50\%, hirsutism in 28\% and
irritability and hyperactivity in 21\% of the patients. Increased body weight was not
prominent and was controlled with dietary measures.
In an other randomised double-blind controlled trial in which alternate-day deflazacort (2.0 mg/kg/d) was given to 28 DMD patients a significant increase in “gait” without clear improvement of muscle force was seen after 6 months of therapy. Reported side effects were behavioural changes (54%), increased appetite (45%) and Cushingoid appearance (18%).

An open trial in which 30 DMD patients aged 7-15 years were treated with 0.9 mg/kg/d deflazacort for 3 years on average, suggested that deflazacort has a long-term beneficial effect on muscle function and respiratory muscle strength. However, side effects such as growth suppression and cataracts did appear.

To reduce the extent of side effects Fenichel tested oxandrolone (0.1 mg/kg/d) in 10 DMD patients aged 6-9 years for 3 months in an open study and reported a significant improvement in muscle strength (modified MRC 1-10) without side effects. Unfortunately, the improvement in muscle force could not be confirmed in a randomised, double-blind controlled trial. There was also no benefit in timed functional tests.

In an interim report in which deflazacort (0.9 mg/kg/d) was compared with prednisone (0.75 mg/kg/d), Reitter concluded that after 3-15 months both steroids seemed to be equally effective in slowing down muscle force deterioration which was later confirmed by Bonifati et al.

**Summary and conclusion**

In the past 3 decades several trials have convincingly demonstrated a short-term beneficial effect of prednisone treatment on muscle force and muscle function in Duchenne muscular dystrophy.

Daily given prednisone 0.75 mg/kg/day appeared to be the lowest effective dose. Even in intermittent schedules, prednisone, 0.75 mg/kg/d during the first 10 days of each month, preserves its beneficial effect.

Side effects are associated with prednisone treatment despite dose reduction and intermittent schedules.

The long-term benefits of prednisone treatment remain unclear since only open trials or pilot trials have been conducted in which the follow-up period was relatively short (1-2 years). Longer follow-up has only been reported in a very limited number of patients. Deflazacort, 2.0 mg/kg alternate day significantly improved timed tests but its beneficial effect over prednisone and its long term benefit remain unclear.

In conclusion, short term intermittent prednisone treatment has a beneficial effect on muscle force and muscle function in ambulant DMD patients. The influence on the quality of life and the long-term outcome with respect to beneficial effects and side-effects are still unknown.
Acknowledgement

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Abbreviations
BP: blood pressure
BT: body temperature
CBC: complete blood count,
CK: creatine kinase
GI: gastrointestinal
HT: hypertension
MRC: medical research council
QMT: quantitative muscle testing
RBC: red blood cell
Sig.: significantly
WBC: white blood cell
Reference List


17. Shakhovskaiia NI, Shishkin SS, Skozobtseva LF et al. The use of low doses of prednisolone for


34. Reitter B. Deflazacort vs. prednisone in Duchenne muscular dystrophy: trends of an ongoing study.


