Deflazacort Use in Duchenne Muscular Dystrophy: An 8-Year Follow-Up

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Data reported here were collected over an 8-year period for 79 Duchenne muscular dystrophy patients, 37 of whom were treated with deflazacort. Mean length of treatment was 66 months. Treated boys stopped walking at 11.5 ± 1.9 years, compared with 9.6 ± 1.4 years for untreated boys. Cardiac function was better preserved with the use of deflazacort, as shown by a normal shortening fraction in treated (30.8 ± 4.5%) vs untreated boys (26.6 ± 5.7%, P < 0.05), a higher ejection fraction (52.9 ± 6.3% treated vs 46 ± 10% untreated), and lower frequency of dilated cardiomyopathy (32% treated vs 58% untreated). Scoliosis was much less severe in treated (14 ± 2.5°) than in untreated boys (46 ± 24°). No spinal surgery was necessary in treated boys. Limb fractures were similarly frequent in treated (24%) and untreated (26%) boys, but vertebral fractures occurred only in the treated group (7/37) (compared with zero for the untreated group). In both groups, body weight excess tripled between the ages of 8 and 12 years. All untreated patients grew normally (>4 cm/year), as opposed to only 15% of treated boys. Deflazacort improves cardiac function, prolongs walking, and seems to eliminate the need for spinal surgery, although vertebral fractures and stunted growth occur. The overall impact on quality of life appears positive. © 2008 by Elsevier Inc. All rights reserved.

Introduction

Duchenne muscular dystrophy is a degenerative disease that usually becomes clinically detectable in childhood, between ages 2 and 4, as a progressive proximal weakness. It is characterized by lack of dystrophin, which seems essential to striated muscle membrane stability. Inheritance is X-linked recessive. No cure is yet available for Duchenne muscular dystrophy, but the use of steroids such as prednisone or deflazacort, a prednisolone derivative, improves strength and maintains pulmonary function [1-18].

Deflazacort has been in use at the Marie-Enfant Rehabilitation Centre of Sainte-Justine Hospital, Montreal, Canada, since 1993, initially in a comparative study with prednisone.

Numerous studies have reported improved strength and mobility in Duchenne muscular dystrophy patients treated with deflazacort [1-18], and some have shed light on improvement in cardiac function [18-20] or on reduction of scoliosis [10,18,21] or have given an overall picture of the positive and negative effects of the drug [10,18]. The present report is based on long-term clinical observations with deflazacort and provides an overview of both positive aspects and unwanted side-effects of this drug.

Patients and Methods

Patients

We reviewed the charts of 105 patients, all boys, followed at the multidisciplinary Neuromuscular Clinic of the Marie-Enfant Rehabilitation Centre, Montreal. In all of these patients, Duchenne muscular dystrophy was diagnosed on the basis of gene deletion or the absence of dystrophin on biopsy.

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Received May 2, 2007; accepted November 12, 2007.
Patients were divided into two groups: those receiving deflazacort for more than 1 year (treated) and those not receiving the drug or who began using it less than 6 months before (untreated). A total of 42 boys had been taking deflazacort for more than 1 year; of these, 4 were excluded because they had used the drug for more than 2 years and then stopped, and 1 was excluded because he had been taking prednisone for 6 years before changing to deflazacort. The final treated group thus comprised 37 patients.

Of the remaining 63 untreated patients, 17 were excluded because of insufficient data and 4 because they were too young to participate in segmental muscle testing or pulmonary function tests. The final untreated group thus comprised 42 patients. Of these, 24 had been followed at the clinic until they were 18 years old and had never taken deflazacort; data were extracted from their charts at different ages, for every visit at the clinic (every six months). Mean age at the last visit was 18.2 ± 2.7 years. The other 18 boys were being actively followed at the clinic. Of these, 11 had never taken deflazacort (because still quite functional or because parents refused), 1 had started the drug less than 6 months before stopping (either because of excessive weight gain or behavioral problems).

The 37 treated boys had a mean age of 13.1 ± 3.2 years; the 18 untreated patients being actively followed at the clinic had a mean age of 9.5 ± 2.9 years. Overall, the study compared 37 treated patients to 42 untreated patients.

**Dose**

Deflazacort was started when boys manifested functional decline rendering ambulation difficult, such as increased effort getting up from the floor, difficulty getting up and down stairs, and increased falls. Deflazacort was begun at 0.9 mg/kg and was adjusted according to evolution or side effects to a maximum of 1 mg/kg. Regardless of deflazacort treatment status, all boys were seen every 3 months by a neurologist, pediatrician, or physiatrist for drug monitoring and every 6 months by the whole team. Elementary calcium 250 mg three times a day and vitamin D 400 IU daily were prescribed as soon as deflazacort was started.

The mean length of treatment with deflazacort was 66 months. Deflazacort was taken by 26/37 patients (70%) for more than 5 years and by 8/37 patients (22%) for more than 8 years. The 3 remaining patients had been taking the drug for less than 5 years. Mean age at beginning of treatment was 7.6 ± 1.7 years. Mean dose at the most recent visit was 0.69 ± 0.2 mg/kg.

**Methods**

Blood pressure, weight, and height were measured at every visit for treated patients. Height was measured by arm span method when a boy could no longer stand. Weight excess was diagnosed when body mass index (kg/m²) exceeded the 85th percentile for age and sex.

Forced vital capacity was measured twice a year with a spirometer (S & M Instruments, Doylestown, PA). The result was compared with the predicted value for height and age as per standards [22]. Strength in terms of manual muscle testing according to the Medical Research Council Scale was measured every 6 months in 34 muscles. Scores were cumulated and converted to a percentage of normal (i.e., with 100% being normal).

Loss of ambulation was recorded as complete when the boy or his family reported that he could no longer walk even with help. For the older patients who used long-leg braces, loss of ambulation was recorded as the time when natural walking stopped or when the use of braces began.

Bone mineral density was measured approximately 2 years after beginning deflazacort and every year thereafter. Bone mineral density was measured by dual-energy x-ray absorptiometry and is expressed as a Z-score that represents a standard deviation for a subject’s bone mineral density relative to age- and gender-matched control subjects. Bone mineral density is considered normal if values fall within two standard deviations of the mean. Osteoporosis is thus diagnosed if Z-score values are below −2.0 or if there is a fracture. Z-scores for the lumbar vertebrae are reported here. Bisphosphonates were introduced if the Z-score was below −3.5 or if a patient had a fracture. Bone mineral density was measured only in treated boys.

Spinal x-rays were taken yearly, once the boys used a wheelchair regularly or if thoracic deformity was noted. Scoliosis is usually defined as a Cobb angle greater than 10° in the coronal plane [23]. If there was a curve greater than 10°, x-ray imaging was repeated every 6 months. Boys were referred for surgery if the spinal curve angle progressed beyond 45° with vital capacity greater than 25%. Limb or supplemental spinal x-rays were taken if patients complained of sudden back or limb pain.

Treated boys were referred to an ophthalmologist after 2 years of treatment, to check for cataract formation. Yearly ophthalmologic consultation was recommended. Cardiac function was assessed via echocardiography every 6 to 12 months. Ventricular strength was measured by the ejection fraction and the shortening fraction, the latter measure representing the difference between the diameter or volume of the left ventricle at rest and during maximal contraction. A shortening fraction greater than 28% and an ejection fraction greater than 55% were considered normal. The data reported by the cardiologist concerns 38 treated and 48 untreated boys from the same population as the rest of the study.

**Statistical Analysis**

Means and standard deviations were calculated for age at loss of walking and scoliosis. Means for vital capacity and strength were obtained for every chronological age. Unpaired t-tests were used to establish whether a significant difference exists between the treated and untreated groups for different variables.

**Results**

**Medication**

Mean deflazacort dose at the end of the study was 0.69 ± 0.22 mg/kg.

**Ambulation**

Twelve of the 37 patients in the treated group had already stopped walking at the time of the study. Mean age at loss of ambulation was 11.5 ± 1.9 years, compared with 9.6 ± 1.4 years (P < 0.05) in the 32/42 untreated patients who had stopped walking.

**Table 1. Muscle strength and vital capacity at age 16 in boys treated and not treated with deflazacort for Duchenne muscular dystrophy**

<table>
<thead>
<tr>
<th></th>
<th>Treated (N = 8)</th>
<th>Not Treated (N = 21)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Muscle strength, %</td>
<td>63 ± 4</td>
<td>31 ± 3</td>
<td>&lt;0.003</td>
</tr>
<tr>
<td>Vital capacity, %</td>
<td>66 ± 14</td>
<td>48 ± 22</td>
<td>&lt;0.007</td>
</tr>
</tbody>
</table>

Treated was defined as having taken deflazacort for >1 year; untreated, as not taking the drug or having begun it <6 months before.
Among patients aged 12 years or older, walking was possible in 13/23 in the treated group (53%) and in none of the untreated group (0/28).

Muscle strength and vital capacity at 16 years of age differed significantly between treatment groups (Table 1). Only 8/37 treated boys were 16 years of age or older, and only 21/42 untreated patients had measurements done at the age of 16.

**Scoliosis**

Scoliosis developed in 10/37 treated patients (27%), compared with 28/42 untreated patients (67%). Degree of scoliosis was 14° ± 2.5° and 46° ± 24° in treated and untreated patients, respectively ($P < 0.05$). Of the 42 untreated patients, 9 (21%) had curves greater than 50°, whereas none of the treated boys had curves greater than 18° (Fig 1). Almost all patients in the older untreated group (22 of 24, or 92%) developed scoliosis greater than 10°. Spine surgery was necessary in 12 of 28 untreated patients (43%). None of the treated patients had to resort to surgery.

**Cardiac Function**

Cardiac dimensions and function in treated and untreated boys were measured over a 3- to 7-year period (Table 2). No change was observed in blood pressure, left ventricle end-diastolic diameter, or cardiac mass (either per se or indexed for body surface). A statistically significant difference was observed for shortening fraction, ejection fraction, and the presence of dilated cardiomyopathy, with better preserved cardiac function in boys using deflazacort. Of note, angiotensin converting enzyme inhibitor was given in both groups, significantly more often in the treated group. We were not able to isolate its effect from deflazacort in this study.

**Fractures**

Both treated and untreated patients had fractures (Fig 2). By type of fracture, 9/37 treated patients (24%) and 11/42 untreated patients (26%) had at least one limb fracture, and 12 vertebral fractures were recorded in 7 treated patients (20%); no vertebral fractures were recorded in the untreated group. Two patients in the treated group had more

| Table 2. Cardiac dimensions and function in boys treated and not treated with deflazacort for Duchenne muscular dystrophy |
|--------------------------------------------------|--------------------------------------------------|--------------------------------------------------|
| **Treated (N = 38)**                              | **Untreated (N = 48)**                             | **P Value**                                      |
| Age, yr                                          | 13.3 ± 4.0                                        | 14.5 ± 3.8                                       |
| Blood pressure, mm Hg                            |                                                   |                                                  |
| Systolic                                         | 108 ± 10                                          | 108 ± 12                                         |
| Diastolic                                        | 66 ± 8                                            | 66 ± 9                                           |
| LV diastole, mm                                  | 44.8 ± 4.8                                        | 48.3 ± 7.5                                       |
| Cardiac mass, gm                                 | 88.1 ± 23.8                                       | 108.4 ± 46.7                                     |
| Indexed cardiac mass, g/m²                       | 74.3 ± 13.3                                       | 74.0 ± 23.8                                      |
| Shortening fraction, %                           | 30.8 ± 4.5                                        | 26.6 ± 5.7                                       |
| Ejection fraction, %                             | 52.9 ± 6.3                                        | 46.0 ± 10                                        |
| Dilated cardiomyopathy,* no. (%)                 | 12 (32)                                           | 28 (58)                                          |
| ACE inhibitor use, no. (%)                       | 19 (50)                                           | 11 (23)                                          |

Except as indicated, values are given as mean ± standard deviation.

* Dilated cardiomyopathy was defined as SF < 28% or LVd > 95th percentile.

Abbreviations:

ACE = Angiotensin-converting enzyme
LVd = Left ventricular end-diastolic diameter
LV diastole = Left ventricular diameter in diastole
SF = Shortening fraction (normal SF ≥ 28%)
than one limb fracture and two others had more than one vertebral fracture. In the untreated group, four patients had more than one limb fracture. Of the 37 treated patients, 16 (43%) had at least one fracture, either vertebral or limb, which is significantly more than the untreated group (11/42 patients, or 26%). Most vertebral fractures (11/12) occurred in boys who had been treated for 5 years or more. Some vertebral fractures were asymptomatic; none were responsible for a functional decline.

We looked at the number of fractures occurring in walking vs nonwalking patients. In the treated group, 20/26 fractures (77%) occurred in patients who could still ambulate independently: 8 vertebral and 12 limb fractures. In the untreated group, in which all fractures were limb fractures, 11/19 fractures (58%) occurred in children who could still walk.

**Bone Mineral Density**

Bone mineral density measurements showed general decline with time as measured in the treated group. Mean Z-score after 1 year of treatment was $-1.8$, compared with $-4.5$ after 7 years (Fig 3). Either alendronate (17 patients) or pamidronate (2 patients) was given to 19 of the 37 deflazacort-treated patients and to none of the untreated patients. These data cannot be compared with the untreated group, however, and the effect of bisphosphonates cannot be isolated.

**Bodyweight and Height**

Weight excess was already present in both groups at 8 years of age, and its frequency tripled at 12 years (Table 3). Slightly more patients had weight excess in the treated group (13/21, or 62%) than in the untreated group (6/11, or 55%) at 12 years of age. The number of patients in each group is smaller than the total number of treated or untreated patients, because some were younger than 12 years of age or, especially in the older untreated patients, because they were not weighed or measured specifically at that age.

Of those for whom data were available, only 3/20 in the treated group (15%) grew 4 cm/year or more, compared with 19/19 in the untreated group. Mean height gain was three times as much in the untreated group at 12 years of age than in the treated group.

**Cataracts**

Cataracts developed in 18 of the 37 treated patients (49%). In almost all of these patients (17/18, or 94%) the cataracts developed after at least 5 years of treatment. Only one patient needed surgery.

**Discussion**

Positive effects of deflazacort in humans have been noted since the very first studies [1-14,19].

Recently, Biggar et al. [18] reported results on the long-term benefits of daily deflazacort, comparing 40 treated boys to 34 boys not receiving the drug. Mean age was 15.2 years in both groups; mean duration of therapy was 5.5 years. Among functional benefits, walking was still possible in 25/31 patients (81%) at age 12 years, in 13/17 patients (76%) at age 15 years, and climbing stairs and rising from the floor in, respectively, 6/17 (35%) and
4/17 (23%) patients at age 15. This differs widely from the natural history of the disease.

The present study compared 37 treated with 42 untreated boys over a period of 8 years. The mean duration of therapy was 5.5 years.

Muscle strength at 16 years of age showed a definite difference between treated (63%) and untreated (31%) groups. This is in accord with the report of Schara et al. [12], who in 26 age-matched treated and untreated boys measured an average muscle strength of 64% (treated) and 20% (untreated).

Vital capacity at 16 years of age was also better preserved in treated (66% of predicted vital capacity) than untreated patients (48% of predicted). Although individual measurements showed high variability, the average vital capacity is in accord with findings of other studies (10,12,18). None of our treated patients required assisted ventilation.

With deflazacort, ambulation was prolonged from 9.6 to 11.5 years. This is less than what has been noted in other studies of deflazacort, in which ambulation stopped at a mean age of 12.8 years [10] or 13 years [12] in treated patients. Nonetheless, half of our treated patients aged more than 12 years (13/23) were still walking, compared with none of the untreated group (0/28) at the same age.

The fact that 7 boys in the untreated group took deflazacort (though for less than 6 months) may have contributed to decreasing the treatment effect seen in the deflazacort group. Another reason for the age discrepancy between the present and previous studies may be that the end-point of walking is not well defined. Cessation of ambulation was not defined in any of these studies. The present number of patients was too small to allow identifying the individual effect of each drug.

The frequency and magnitude of scoliosis were also definitely improved in treated patients. Scoliosis occurred in 27% of treated vs 67% untreated patients, with a mean curve measuring 14° vs 46°, respectively. Alman et al. [21] and Biggar et al. [10] also reported lower frequency and magnitude of spinal curvature in patients using deflazacort. In the Balaban et al. [24] study, 10/19 control subjects (53%) resorted to back surgery, whereas 2/15 prednisone treated-boys and none of the 12 deflazacort treated boys required surgical intervention [24]. In contrast to some of these studies, none of our deflazacort patients had to resort to surgery. This differs sharply from untreated historical cohorts, among whom scoliosis developed in 85-100% of cases [26].

In the treated boys, growth appeared to be drastically slowed. Only 15% of our treated patients grew more than 4 cm/year, compared with 100% of untreated patients.
Normal growth in children before puberty is at least 4 cm/year.

In the present study, therefore, 85% of treated boys showed abnormal growth. Biggar et al. [10,18] and Hawker et al. [27] also reported height being much less in treated adolescents, as did Schara et al. [12], who reported short stature present in three fourths of treated boys. Although the natural evolution of Duchenne muscular dystrophy is accompanied by slowed growth, with many patients measuring below the 50th percentile for height [26,28], deflazacort slows growth even further.

Weight excess occurs naturally in Duchenne muscular dystrophy [26]. McDonald et al. [26] reported on 162 boys who were followed prospectively and had not received steroids. From ages 9 to 13, 44% of subjects were above the 90th percentile for weight. Before age 9, weight was normally distributed.

We chose to report on body mass index instead of weight percentiles, to account for stunted growth. Weight excess (body mass index > 85% percentile) was already present at 8 years of age in 26% of treated and 17% of untreated patients. In both groups, however, weight excess increased in frequency at 12 years (62% treated vs 55% untreated). This is similar to findings of Schara et al. [12], who reported obesity being present in both treated and untreated patients. Alman et al. [21] did report weight excess in the treated group, but in comparison with a control group that was 2 years older, which may be confounding, given that steroid-free Duchenne patients usually lose weight at adolescence. Dietary efforts aiming at weight control appear to be of utmost importance in both treated and untreated patients [10,13,26].

Bone mineral density measurements declined with duration of therapy (−1.8 at 1 year, −4.5 at 7 years). It is known that osteoporosis occurs in Duchenne muscular dystrophy even without the use of steroids [29]. Bianchi et al. [30] measured bone mineral density in 32 10-year-old Duchenne muscular dystrophy patients, 22 of whom had been taking prednisone for an average of 38 months. Bianchi’s group showed that both bone mineral density and vertebral Z-score were significantly lower in steroid-treated boys. In the present study, bone density data were acquired only in treated patients, and so the effect of bisphosphonates cannot be isolated.

Fractures do occur in steroid-free Duchenne muscular dystrophy patients [29,31]. McDonald et al. [32] reported on 378 Duchenne muscular dystrophy patients in whom, retrospectively, a fracture rate of 20.8% was found. There was no difference between the fracture rate of patients previously or currently exposed to steroids and that of patients who had never used the drug (20.5% vs 21.1%). No vertebral fractures were recorded [32].

In the present study, we found a limb fracture rate of 24% in treated and 26% in untreated boys. Treated boys usually have more severe osteoporosis and also walk for a longer period, two factors that can contribute to an increased fracture rate.

Vertebral fractures appear to be related strictly to deflazacort use: none occurred in untreated patients, but 19% of treated patients developed vertebral fractures. To our knowledge, no similar fracture rate has been reported previously. The present study did not, however, engage in systematic screening for fractures: x-rays were taken yearly for scoliosis detection or if boys complained of backache. Vertebral fractures were noted in a case report by Talim et al. [33] in a 14-year-old boy who had been taking deflazacort for 7 years. Alman et al. [21] mention only one case of vertebral fracture among a group of 30 treated patients.

Finding vertebral fractures with steroid use is not surprising, given that vertebrae are made up of 70% trabecular and 30% cortical bone. Trabecular bone has an increased turnover, so it is more susceptible to metabolic effects of drugs such as steroids.

Notably, however, vertebral fractures never led to functional loss in our patients, which is unlike limb fractures. Back pain due to fractures was controlled by either a short-term use of narcotics or a single IV dose of bisphosphonates. Boys maintained the ability to walk, transfer, and propel a wheelchair as before.

Hawker et al. [27] reported on a 2-year stabilization of the Z-score with alendronate given as soon as the Z-score fell below −1.0 in 16 deflazacort-treated boys. This points toward a recommendation to begin bisphosphonates earlier.

The number of patients with cataracts increases with duration of therapy. Cataracts in the present study occurred mostly after 5 years of deflazacort use; examination for cataracts was not performed before 2 years of steroid use. Half of the patients on deflazacort developed cataracts. Schara et al. [12] found that 14 of 19 patients developed cataracts between 12 and 64 months of deflazacort use; only one resorted to surgery. Biggar et al. [10] found asymptomatic cataracts in 10 of 30 boys, mostly within 3 years of deflazacort use.

Cataracts have also been reported with prednisone use [4,11,17].

Conclusion

Based on observations over an 8-year period, deflazacort use in Duchenne muscular dystrophy prolongs walking by at least 2 years, slows the decline of vital capacity, and postpones the need for mechanical ventilation. An improved cardiac function, lesser scoliosis, and no need for spinal surgery are other positive effects of deflazacort. Although not measured explicitly, quality of life seemed improved in terms of prolonged independence in transfers and rolling over in bed, as well as sitting comfortably without having to resort to surgery.

Only vertebral fractures (as opposed to limb fractures) were more frequent with deflazacort, and these caused no increased handicap.

Even though weight excess was only slightly more present with deflazacort, the combination of increased...
weight, rounded facies, stunted growth, and a persisting prepubertal appearance typically has an effect on a boy’s body image. It would be worthwhile to investigate the psychological impact of this unsought-for shift from normal maturation.

Dietetic vigilance even before deflazacort is introduced would probably help reduce weight gain, and earlier use of bisphosphonates may help reduce osteoporosis. Thus, given the many positive aspects of deflazacort, it seems worthwhile to refine treatment strategies to lessen its side effects.

The authors give many thanks to Alain Naud, Annie Besner, and Noëlla Shorgan.

References