Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade

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Abstract

We compare the clinical course of 74 boys 10–18 years of age with Duchenne muscular dystrophy (DMD) treated (40) and not treated (34) with deflazacort. Treated boys were able to rise from supine to standing, climb stairs and walk 10 m without aids, 3–5 years longer than boys not treated. After 10 years of age, treated boys had significantly better pulmonary function than boys not treated and after 15 years of age, 8 of 17 boys not treated required nocturnal ventilation (treated 0 of 40). For boys over 15 years of age, 11 of 17 boys not treated required assistance with feeding compared to none of the treated boys. By 18 years, 30 of 34 boys not treated had a spinal curve greater than 20° compared to 4 of 40 treated boys. By 18 years, 7 of 34 boys not treated had lost 25% or more of their body weight (treated 0 of 40) and 4 of those 7 boys required a gastric feeding tube. By 18 years, 20 of 34 boys not treated had cardiac left ventricular ejection fractions less than 45% compared to 4 of 40 treated boys and 12 of 34 died in their second decade (mean 17.6 ± 1.7 years) primarily of cardiorespiratory complications. Two of 40 boys treated with deflazacort died at 13 and 18 years of age from cardiac failure. The treated boys were significantly shorter, did not have excessive weight gain and 22 of 40 had asymptomatic cataracts. Long bone fractures occurred in 25% of boys in both the treated and not treated groups. This longer-term study demonstrates that deflazacort has a very significant impact on health, quality of life and health care costs for boys with DMD and their families, and is associated with few side effects.

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Duchenne muscular dystrophy (DMD) is a recessive X-linked inherited disorder affecting primarily skeletal and cardiac muscle. It occurs in 1 in 3500 male live births. Boys with DMD exhibit a progressive and predictable loss of muscle function [1–4]. As young boys, walking may be delayed and awkward. They have difficulty climbing stairs, rising up from the floor to standing and most are unable to run normally. Although variable, most boys lose ambulation by 7–12 years (average 10 years) [1–5]. Progressive loss of respiratory function usually begins early in the second decade and progresses to respiratory failure and the need for nocturnal ventilation in their mid to late teens [1,6–10].

Scoliosis develops in most boys, usually 3–5 years after they become full-time wheelchair users [11]. After scoliosis surgery, most boys will need assistance with feeding. Severe weight loss may occur in some boys during their mid to late teens and these boys frequently require the use of supplemental gastric tube feedings [1]. Cardiomyopathy, often associated with few symptoms, is common in their second decade [1,3,12–14]. Death frequently occurs in their late teens and twenties from respiratory and/or cardiac complications. Aggressive respiratory management does have a significant impact on their life expectancy [15]. Today, there is no cure for this disease. Corticosteroids offer the only method of preserving muscle function [16–20]. Their mechanism(s) of action is unknown. Several hypotheses for this have been proposed [19]. A general consensus is that daily corticosteroids should be offered to boys while they are still ambulating [19,20]. Two corticosteroids, prednisone (0.75 mg/kg per day) and deflazacort (0.9 mg/kg per day) have been used extensively.
They appear to be equally effective in preserving skeletal muscle function. Both drugs are associated with side effects. Excessive weight gain can be particularly troublesome but deflazacort appears to be associated with less weight gain than prednisone [16]. Because excessive weight gain can impact negatively on their muscle function, we have routinely offered deflazacort treatment for boys with DMD. We report here our clinical observations using deflazacort treatment in boys who were between 10 and 18 years of age and who had started deflazacort between 6 and 8 years of age and have continued taking deflazacort for at least 2 years.

1. Patients and methods

1.1. Patients

All 74 boys who met the following criteria were included: between 10 and 18 years of age, diagnosed with DMD, could cooperate for reproducible muscle and pulmonary function testing and were followed in our comprehensive neuromuscular clinic between January 1990 and December 2004. All patients fulfilled the following five diagnostic criteria for DMD: (1) onset of weakness before 5 years of age, (2) male sex, (3) proximal muscle weakness, (4) increased serum creatine kinase, and (5) a muscle biopsy and/or dystrophin analyses consistent with DMD or DNA mutation and analysis by PCR or Southern blot techniques to detect gene deletions. Boys were given the option of deflazacort treatment when they were ambulatory and when there was early clinical evidence of decreasing muscle function. This was usually indicated by parents reporting that their son was falling more frequently, having more difficulty getting up to standing after falling and climbing stairs. Information about deflazacort was shared both verbally and in writing. Some of the boys have been described in previous publications [21–24].

Forty were treated with deflazacort; 34 were not. Their height, weight and pulmonary function were similar for both groups prior to starting deflazacort. All 74 boys were walking at 7 years. Most boys who were not treated with deflazacort were those boys whose families declined deflazacort because of their fear of possible side effects or for cultural and religious beliefs or boys who were followed before deflazacort was routinely offered as treatment (1993). They were followed by the same multidisciplinary team and with the same clinical protocol. The initial dose of deflazacort was 0.9 mg/kg per day. This was usually taken at breakfast. The boys treated with deflazacort were given daily oral supplements of vitamin D (1000 units) and calcium (750 mg).

Most boys, not treated with deflazacort, also took supplemental vitamin D (400 units) and calcium (250–500 mg). The milligram per kilogram per day dose of deflazacort gradually declined over time as the boys grew and gained weight and/or was reduced because of side effects. By 10 years of age, the mean dose was 0.8 ± 0.18 mg/kg per day, by 15 years it was 0.55 ± 0.09 and by 18 years 0.5 ± 0.2 mg/kg per day.

1.2. Methods

Patient monitoring in both treated and not treated groups was normally done every 4–6 months using a standard clinical protocol. The clinical data were reviewed retrospectively. Muscle function was evaluated by historical information and by direct observation of the following three functions: climbing four standard stairs (17 cm) with a railing, rising up from supine to standing and walking 10 m on a level floor without aids. End points for each were: not able to climb stairs, not able to rise from the floor independently and not able to walk independently. All patients underwent a complete cardiac clinical evaluation every 12–24 months, including a 12-lead electrocardiogram, and a transthoracic echocardiogram. Cardiac size and function were assessed by echocardiography. Left ventricular fractional shortening was calculated using previously described methods [25]. Left ventricular systolic function (ejection fraction) was also assessed visually and graded as normal or impaired (ejection fraction <45%) [26]. All measurements were compared with age-based normal values [27]. If transthoracic echocardiograms were not interpretable, then radionuclide angiography was performed.

Pulmonary function testing as forced vital capacity (FVC) was determined with an electronic spirometer. This spirometer, in our laboratory, gives values similar to the standard values of a Stead-Wells spirometer [7]. Percent predicted values for FVC (FVC-PP) were calculated based on normal published values [8]. The testing was usually performed by the same person to enhance patient cooperation and reduce inter-observer variability. The best of three trials was recorded. A sleep study was normally first performed when the FVC was <1000 cc or if there were symptoms to suggest nocturnal hypoventilation. A sleep study was repeated every 6–12 months. Nocturnal ventilation was usually recommended when the FVC-PP was <20% and/or the nighttime transcutaneous PC02 was >50 mmHg. Clinical side effects data included documenting height, weight, blood pressure (sitting), an eye examination and questions about possible side effects. Clinic visits included independent clinical evaluations by a nurse, physiotherapist, occupational therapist and physician. Boys on deflazacort were evaluated by an ophthalmologist yearly. The clinic nurse gave dietary recommendations to all boys on each visit. Individuals were cautioned that their appetite could increase dramatically after starting deflazacort. Their weight may increase as their activity levels decrease. They should make healthy food choices and consume low fat dairy products. We recommend that they increase their fibre and water consumption and do not add...
Salt to their food. A ‘treat’ is allowed once a week on a designated day. Compliance can be variable from boy to boy, family to family and time to time within the same family. A referral to a nutritionist was made if their weight exceeded their expected weight by 5–10% or if weight loss exceeded 10%. Discussion about surgery for scoliosis began when the boys could no longer ambulate. Spine radiographs were only done if there was clinical evidence of scoliosis or if there was back pain. Surgery was usually recommended when a progressive spinal curve greater than 20° developed and their FVC-PP was greater than 40% [23].

1.3. Laboratory evaluation

Blood specimens for fasting blood glucose, complete blood count, calcium, phosphorus, bilirubin and albumin were obtained every 18–24 months. Urine was tested for glucose by Dipstix yearly. Testing was usually done in a medical laboratory close to the clinic.

1.4. Statistical analysis

Data analysis was performed using the SPSS package (SPSS 2000, Version 12.0.1; SPSS Inc., Chicago, Illinois) [28]. Data are presented as mean ± 1 SD. Fisher’s exact and Student’s t-tests were used to compare baseline variables in patients treated with and without deflazacort as appropriate. The level of significance was set at 0.05 (2-sided).

2. Results

Seventy-four boys met the inclusion criteria, 40 in the deflazacort group (mean age 15.2 ± 2.7 years) and 34 in the not treated group (boys not treated with deflazacort) (mean age 15.2 ± 2.5 years). The mean age of starting deflazacort was 7.7 ± 1.2 years. The mean time on deflazacort was 5.5 years.

2.1. Motor function

Two motor functions, able to rise from the floor and walking 10 m are summarized in Fig. 1.

2.2. Able to rise from the floor

For the treated boys, 28 of 40 (70%) could rise from the floor to standing at 10 years of age, 15 of 31 (48%) at 12 years, 4 of 17 (23%) at 15 years and none at 18 years of age. By contrast, 6 of 34 boys (17%) not treated could rise from the floor at 10 years and none of 28 at 12 years of age.

2.3. Climbing four stairs

For the treated boys, 28 of 40 (70%) could climb four stairs at 10 years of age, 17 of 31 (55%) at 12 years, 6 of 17 (35%) at 15 years and 1 of 6 boys at 18 years of age.

2.4. Walking

All boys treated with deflazacort could walk 10 m at 10 years of age, 25 of 31 (81%) at 12 years, 13 of 17 (76%) at 15 years and 2 of 6 boys walked independently at 18 years of age. By contrast, all 34 boys not treated stopped walking by 12 years of age (mean age 9.8 ± 1.8 years).

2.5. Pulmonary function

The FVC-PP for each group is summarized in Fig. 2. Both groups of boys, treated and not treated, had similar FVC-PP before 10 years of age. At 10 years of age, the FVC-PP in treated boys was 95 ± 14% vs. boys not treated 65 ± 13%, (P < 0.05). At 15 years of age, the FVC-PP in the treated group was unchanged, (88 ± 12%) while the boys in the not treated group had fallen to 47 ± 19% (P < 0.05). By
18 years of age, the FVC-PP in the treated group was significantly greater than boys not treated 81 ± 13% vs. 34 ± 10% (P < 0.05). Also, by 18 years of age, 46% of boys not treated required nocturnal ventilation compared to none of the boys treated with deflazacort.

2.6. Cardiac function

All patients underwent a complete cardiac evaluation every 12–24 months. (Table 1). Left ventricular systolic function was assessed by echocardiography in 95% of patients and by radionuclide angiocardiography in 5%. Four of 40 boys treated with deflazacort had moderate or severe left ventricular systolic dysfunction (ejection fraction < 45%). Twenty of 34 (58%) boys not treated had moderate or severe left ventricular systolic dysfunction (ejection fraction < 45%). Mean percent fractional shortening was 33 ± 7% for treated boys and 21 ± 8% for boys not treated (P < 0.002). Two of 40 boys treated with deflazacort died of left ventricular failure at 13 and 18 years of age.

2.7. Scoliosis

By 18 years of age, (mean 13.8 ± 1.6 years) 30 of 34 (90%) boys not treated had developed a spinal curve > 20% compared to only 4 of 40 (10%) treated boys. Following spinal surgery, 19 of 30 (64%) boys not treated required assistance with feeding by 14.3 ± 1.5 years. The four boys who were treated with deflazacort and who developed a scoliosis requiring surgery could still feed themselves.

2.8. Survival

Twelve of 34 (35%) boys not treated died in their second decade (17.6 ± 1.7 years) of cardiorespiratory complications. Two of 40 boys (5%) treated with deflazacort died at 13 and 18 years of age with left ventricular failure.

2.9. Side effects

2.9.1. Height

At 10 years of age, the treated boys were significantly shorter (128 ± 5 cm) than boys not treated (135 ± 6 cm) (P < 0.05). At 15 years, the treated boys were 143 ± 9 cm tall compared to 164 ± 8 cm for boys not treated (P < 0.005). This significant difference was also observed at 18 years of age (treated 156 ± 7 cm; not treated 166 ± 7 cm) (P < 0.05).

2.9.2. Weight

The mean weight:age for boys treated with deflazacort remained between the 25 and 75th percentile for weight (kg) between 10 and 18 years (10 years, 34 ± 4 kg, 15 years, 58 ± 6 kg and 18 years, 71 ± 8 kg). Boys not treated tended to weigh (kg) more at 10 years (37 ± 6 kg, 75th percentile). In their early to mid teens, the weight of boys not treated plateaued at 52 ± 12 kg (75th percentile) at 13 years, 52 ± 15 kg (25–50th percentile) at 15 years and 53 ± 12 kg (3–10th percentile) at 18 years. By 18 years, 7 of 34 (20%) of boys not treated had lost approximately 25% of their body weight. Of those with the severe weight loss, 4 of 7 required a gastric feeding tube.

2.9.3. Cataracts

Twenty-two of the 40 boys treated with deflazacort developed bilateral cataracts. Cataracts were noted as early as 4 months after starting deflazacort and as late as 10 years. Other side effects were not more prevalent in these 22 boys. That is, they were not the shortest boys or the boys with the most weight gain. The cataracts were asymptomatic in all 22 boys. Intraocular pressures and visual acuity remained normal. None of the boys not treated has developed cataracts.

2.9.4. Other side effects

All 74 boys had normal systolic and diastolic blood pressures. In addition, throughout the study period, there was no glucosuria, and only occasional acne and/or excessive hair growth reported. There was no apparent increased susceptibility to infection or bruising. Gastrointestinal complaints were not more common and no gastrointestinal bleeding was reported. Blood specimens for fasting blood glucose, complete blood count, calcium, phosphorus, albumin, and bilirubin were all within normal limits. Long bone fractures were documented in 25% of all boys treated with deflazacort and not treated. When possible, fractures were treated with internal fixation and early weight bearing. If a leg fracture occurred in their teen years, only 30% of the boys regained ambulation. If a leg fracture occurred in their pre-teen years, more than 80% of the boys regained ambulation. Three boys treated with deflazacort and none of the not treated boys experienced fragility vertebral fractures.

3. Discussion

Until there is a cure for this fatal genetic disorder, the mainstays of treatment include corticosteroids, surgery when needed and comprehensive medical and physical rehabilitation with a focus on cardiorespiratory health.
There is general agreement that boys with DMD benefit from corticosteroid treatment. [16–20]. Daily treatment with prednisone (0.75 mg/kg per day) or deflazacort (0.9 mg/kg per day) [24] seems to offer the most effective treatment when the boys are still walking. Historically, there has been a reluctance to use corticosteroids because side effects are common. Several different protocols for corticosteroid administration are in use [20]. Some centres discontinue corticosteroids when the boys stop walking. We continue deflazacort as long as the benefits outweigh the side effects.

The most effective dose of prednisone or deflazacort for treating boys in their teens is not established. The issue of adjusting the dose of deflazacort (mg/kg per day) as the boys get older is complex but very important. The body weight of boys with DMD can vary significantly even without corticosteroid treatment. This is relevant since the dose of deflazacort is often based on body weight. In general, there are three profiles for weight gain in the first decade. One group of approximately 15–20% of boys with DMD, weighs less than the 10th percentile. These boys do not usually experience excessive weight gain with or without deflazacort treatment. They maintain their deflazacort dose at 0.9 mg/kg per day well into their teens until their weight is approximately 40 kg and their dose of deflazacort is 36–39 mg/kg per day. In contrast, a second group of 40–50% of boys with DMD is at the 50th percentile when they are 5–7 years but their weight increases dramatically to more than the 90th percentile as the boys become less active. There may be a family history of obesity. If these boys are given deflazacort, it is very difficult to know if their weight gain is caused by the deflazacort or if it would have occurred without deflazacort. In either case, correctly or not, the weight gain is usually attributed to the corticosteroids. For these boys, the dose of deflazacort is often less than the 0.9 mg/kg per day and less than the boys in groups 1 and 3. Strict dietary control in this group has some, but often-limited success in controlling their weight. A third group, whose weight between 5 and 7 years is at the 50th percentile is, with strict dietary management, able to maintain their weight between the 25th and 90th percentile after 7 years and their dose of deflazacort ranges between 0.7 and 0.9 mg/kg per day until they receive 36–39 mg/day of deflazacort. Further studies are needed to determine the optimal age to begin corticosteroid treatment and the optimal dose over their lifetime.

Our observations reported here provide new information concerning the risks, harms and benefits of long-term, daily deflazacort treatment to the natural history of this relentless, progressive and fatal disease. The aspects of the natural history we report here include motor, pulmonary and cardiac functions, spinal alignment, ability to self-feed and mortality in the second decade.

Motor function, described here as the ability to climb four stairs, rise from the floor to standing and walk 10 m independently without aids, is preserved significantly in boys treated with deflazacort. With deflazacort, mobility continues 3–5 years longer. Similar observations were reported in 19 boys treated for more than 2 years with 0.9 mg/day of deflazacort [29]. The two boys who were walking at 18 years were not unusual in their clinical presentation. That is, they presented with proximal muscle weakness at 2 and 4.5 years of age. They had abnormalities demonstrated in their dystrophin gene (one with a deletion of exons 51–52 and the other with a duplication) and no demonstrable dystrophin in two muscle biopsies in one boy and one biopsy in the other boy. Deflazacort treatment was started at 7 and 9 years of age. Boys with significant cognitive delays, who are not reported here because they give inconsistent testing scores, are often less motivated to walk, and on average, stop walking earlier. Also not reported here are 4 boys who stopped taking deflazacort within 2–3 years of starting and before they were 10 years old. Three stopped because of behavioural concerns and one because of excessive weight gain. All 4 boys had significant developmental delays and behavioural issues before starting deflazacort.

Respiratory muscle weakness contributes in a major way to the morbidity and mortality in DMD. Pulmonary function follows three typical phases: ascending, plateau and descending [6]. The descending phase typically begins around 10–12 years of age [9]. The rate of decline of percent predicted FVC varies between 5 and 10% per year [1,10]. Our findings in the 34 boys not treated with deflazacort are similar to these published findings. By contrast, boys on deflazacort had no significant decline in their mean FVC-PP between 10 and 15 years and a slight but insignificant decline by 18 years of age. Benefits in pulmonary function were also reported in 30 boys with DMD treated with 0.5–1.0 mg/kg per day of deflazacort [30] and 19 boys on 0.9 mg/kg per day of deflazacort [29]. Of the 34 boys not treated with deflazacort, 46% required nocturnal ventilation by 18 years of age. Their FVC was $22 \pm 10\%$ when ventilation was started. By contrast, none of the treated boys required nocturnal ventilation. Thus, with long-term deflazacort administration and aggressive pulmonary care [15] the natural history for the pulmonary component of DMD has been improved dramatically. In addition, with this improved pulmonary function, there has been a significant impact on their quality of life with fewer admissions to hospital for pulmonary infections and reduced health care costs. Furthermore, in those few boys where we have started deflazacort treatment after they lost ambulation, their pulmonary function improved and the expected rate of decline in FVC-PP was reduced [31].

Deflazacort appears to reduce the prevalence of cardiomyopathy in boys with DMD in their second decade. [22] In this series of patients with DMD, the prevalence of cardiomyopathy in untreated patients was 58%. In other studies that have examined cardiac function in patients with DMD, prevalence rates have been variable [32–36]. In a group of patients similar in age to the patients reported here, Ramaciotti [36] found a similar prevalence of abnormal cardiac function (53%) in their cohort of patients with
DMD. We did not examine for differences in regional wall motion abnormalities [37–39].

It is possible that with newer technologies for assessing cardiac muscle function, changes may be demonstrated when the boys are younger and at a time when the echocardiograms show no apparent abnormality [40,41]. Further studies are needed to determine the impact of these early changes in cardiac muscle and if therapeutic intervention at this young age will impact on the evolution of cardiomyopathy. It is also possible that a significant preservation of cardiac function will be realized by a combination of corticosteroids and standard cardioprotective medication(s).

Scoliosis progresses relentlessly in 90% of boys with DMD [11]. Surgical treatment includes a posterior spinal arthodesis with segmented instrumentation usually to the pelvis [42,43]. Very few boys treated with deflazacort developed scoliosis at the expected age of 13–15 years. The long-term prognosis for spinal alignment in these boys once skeletal maturity is achieved is unclear. Scoliosis might develop in their later years. Alternatively, it may be similar to those who become paraplegic after a spinal cord injury in that scoliosis might occur in skeletally immature individuals but is less likely to occur in skeletally mature individuals [44,45]. In the few treated boys who did require spine surgery, the surgical procedure and postoperative recovery were uncomplicated. Of importance was the observation that most boys who were not treated with deflazacort required assistance for feeding after scoliosis surgery. This reached 64% by 18 years of age. By contrast, all 4 boys who were treated with deflazacort remained independent for feeding after spine surgery.

Asymptomatic cataracts were documented in 22 of the 40 treated boys. None of the boys has required cataract surgery. In our experience, most cataracts were documented within 3–5 years of starting treatment but as late as 10 years.

Although boys with DMD might be shorter than normal [1], boys treated with deflazacort were significantly shorter than boys not treated. This remained significant throughout the 2nd decade. Similar observations have been reported previously with daily deflazacort [30] but there was less impact on height if boys were treated with 20 days of 0.6 mg/kg per day and nothing for the following 10 days [24]. However, we do feel that there is a mechanical advantage to being short [21,46,47]. Still, we do acknowledge that some of the boys, if given a choice, would rather be tall than short.

In summary, these long-term observations are most encouraging. The major benefits of daily deflazacort appear to be prolonging ambulation, improved cardiac and pulmonary function, delaying the need for spinal instrumentation and greater independence for self-feeding. The impact on quality of life issues for the boys and their families, although not measured specifically in these boys, is likely significant. Health care costs during this time interval are reduced significantly for example by avoiding spine surgery and associated rehabilitation, delaying the need for nocturnal ventilation and delaying the need for assisted care.

There are, however, some limitations to our report. The study is retrospective. The boys not treated were a convenience sample of boys not treated with deflazacort and the similarity of the two groups at baseline may be in question. However, boys in both groups could walk at age 7. It is also reassuring that pulmonary function, which is representative of overall muscle strength, was similar at baseline. The heights and weights for both groups were also similar. They were monitored with a similar protocol.

Important questions remain unanswered. How long will the benefits of deflazacort reported here continue? What is the best age to start corticosteroid treatment? How do corticosteroids work and what is the optimum dose throughout their lifetime? What are the benefits if corticosteroids are started after the boys stop walking?

The natural history of DMD is changing under the influence of corticosteroids. There are benefits and side effects. But while we wait for a cure or a better treatment program for this progressive and fatal disease, corticosteroids offer time and hope for these boys and their families.

References


