Efficacy of corticosteroid in decreasing scoliosis and extending time to loss of ambulation in a single clinic: an effectiveness trial

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Abstract

Purpose: Pharmacologic doses of corticosteroid (CS) have been shown to ameliorate the progression of Duchenne muscular dystrophy (DMD) preserving strength, pulmonary function and ambulation as well as reducing the incidence of scoliosis. However, there are serious side effects of CS, which may impact dose tolerance. The purpose of this study was to compare the magnitude of positive CS effects on patients in our clinic to those reported in the literature.

Methods: We retrospectively reviewed medical records and radiographs of 142 DMD patients who were seen between 1st January 1991 and 31st December 2017.

Results: In total, 101 boys met study inclusion criteria. Of these 32 were steroid naïve, 37 took the recommended dose (standard of care, SOC) of Prednisone or Deflazacort, and 32 took a lower dose (LD). Following initiation of CS, both treatment groups showed an increase in weight velocity and decrease in linear growth velocity. Although there was a trend to later loss of ambulation (LOA) in the SOC group relative to the naïve group by one year, this was not significant, however, a small subgroup of boys on Deflazacort showed a 3.4 year later LOA than the naïve group. The incidence of scoliosis was reduced from 69% in the naïve, to 41% in the LD and 47% in the SOC group.

Conclusions: Although there was a reduction in the incidence of scoliosis, it was not as robust as seen elsewhere. Many published studies have inadequate data on scoliosis probably due to the lack of inclusion of orthopaedists in the study group.

Level of evidence: IV

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Introduction

Duchenne muscular dystrophy (DMD) is an X-linked recessive disorder characterized by progressive muscle weakness due to absence of the muscle protein dystrophin. Natural history studies have shown that untreated boys lose the ability to ambulate beginning at age eight years, and all will be non-ambulatory by their 12th birthday.1–7 Around the time of the loss of ambulation (LOA), up to 90% develop scoliosis between the ages of 10 and 12 years, and require spinal fusion to prevent progressive deformity.6,8,9 Prior to the introduction of corticosteroids, life expectancy was late teens or early twenties and death was typically caused by respiratory failure.10

Corticosteroid (CS) therapy for DMD was first proposed in 1974 by DeSilva,11 but did not become generally accepted as a therapy for DMD until the 1990s, following a multicentre study by the Clinical Investigation of Duchenne Dystrophy group, which reported a beneficial impact on muscle strength.12 Even so, CS did not become standard of care (SOC) until the 2000s, after studies demonstrated positive multisystem functional effects in patients with DMD.13 Currently CS therapy, either Prednisone, Prednisolone, or Deflazacort is prescribed as early as four years of age; however, many clinicians wait until physical function plateaus or begins to decline, usually around six to seven years of age, to initiate use.14,15 Although the mechanism of action of CS is unclear, it has been shown to slow the progression of muscle weakness, and thereby lengthen

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the period of ambulation, slow respiratory and cardiac decline, and decrease the incidence of scoliosis.1,7,8,10,16-28

With regard to scoliosis there are several single-centre reports that report a dramatically reduced incidence1,8,22,23,25,29 in boys with DMD using the CS Deflazacort, in addition to confirming the other beneficial effects of CS. Furthermore, the rate of scoliosis surgery for boys with DMD in the United States declined by 48% from 2001 to 2012, coincident with the increased prescription of CS, indicating the effectiveness of CS in prevention of scoliosis.26 Although there are many reports of the positive effects of Prednisone and Prednisolone on providing prolongation of ambulation and preservation of pulmonary function, there are no definitive reports of these CS alone on reducing the incidence of scoliosis in patients with DMD.

The purpose of this retrospective cohort study was to determine how effective our clinical administration of CS to boys with DMD in our Muscular Dystrophy Association (MDA) clinic was in prolonging ambulation and preventing the development of scoliosis in comparison to previously reported results from single centres.1,8,22,23,25,29 Boys were prescribed either Deflazacort (when possible) or Prednisone to a diverse ethnic population, with the focus on clinical care, without a prospective research component. This study is classified as an ‘effectiveness trial’ to assess the effect of these medications in a ‘real world’ setting, as opposed to an ‘efficacy trial’ which reports the ‘performance of an intervention under ideal and controlled circumstances’.30

Materials and methods

A retrospective chart review was performed of a single institution’s multidisciplinary MDA neuromuscular clinic patient population from 1st January 1991 and 31st December 2017. The study was reviewed and approved by the Institutional Review Board of Oregon Health and Sciences University. Inclusion criteria for this analysis were: clinical characteristics of DMD, male, between the ages of four to 21 years, with sufficient information in the clinical record defined as a minimum of 20% of the required elements, and a positive test for DMD by either DNA analysis or muscle biopsy (used prior to the availability of DNA diagnosis). Boys in clinical trials of new medications such as molecular modifiers (Exondys, Ataluren, etc.) or other innovative drugs (Cialis) were excluded. Relevant information was extracted from records up to 21 years of age, which is the maximum age of patients followed in our hospital.

Boys were usually seen every six months in a multidisciplinary MDA clinic, and demographics, height, weight, ambulation status, surgical dates and steroid use were collected from the subjects’ medical records, and scoliosis was ascertained and measured from spinal radiographs. For boys with knee or ankle contractures, or unable to stand, height was measured by arm span or addition of segments.

Boys were divided into three groups:

• Naïve: The steroid naïve group had no history of corticosteroid use.
• Low Dose (LD): Suboptimal steroid group. This group included boys who did not tolerate SOC doses, usually due to behavioural issues or excessive weight gain. At the family’s request, prescribed doses were reduced, or discontinued entirely after taking it initially for at least six months. Less than 20 mg/day was considered as falling into this group.
• Standard of Care (SOC): This group includes boys who received SOC steroid dose, had been taking steroids for a minimum of six months, and were self-reported or parent-reported compliant with their medication regimen. Although the generally recommended SOC is 0.75 mg per kg per day of Prednisone or 0.90 mg per kg per day of Deflazacort up to a 30 mg per day maximum on a daily basis,6,25 for this study > 20 mg/day was considered compliant with SOC. In general, initiation of steroid use was recommended around age seven years, and corticosteroid prescription started in the early 2000s to all DMD patients when data regarding the functional benefits of corticosteroid was clearly demonstrated.13 In the early years, some parents were sceptical of the benefits and concerned about the side effects, and declined treatment; however, currently most families choose to try treatment. Boys were started on Deflazacort when it was possible financially for parents to obtain this medication, which was usually by mail order from the United Kingdom at that time. Some boys were on Deflazacort exclusively, and some had begun on Prednisone and were switched to Deflazacort due to unacceptable side effects.

Boys were considered non-ambulatory (LOA) when it was reported in their medical record. Compliance with prescribed dosage was based on patient or parent-reported statements in the medical record. For patients who reported medication non-compliance, the primary reason was recorded, if available.

Height and weight velocities were calculated for both pre- and post-steroid time frames using three points from the medical record: T1 – first visit to the institution, T2 – visit that steroids were initiated, and T3 – the last visit prior to turning 14 years old to ensure this assessment occurred while boys were still in the linear aspect of their growth curve. See formula below. In the Naïve group, T2 was set at 8.8 years, which was the average age that boys in the steroid group had treatment initiated. The pre-steroid prescription time frame was defined as the duration of time between T1 and T2. The post-steroid time frame was defined as duration of time between T2 and T3.
For assessment of scoliosis, radiographs were initially obtained when there was clinical evidence of scoliosis, and thereafter as needed. Cobb angle was measured by a single experienced pediatric orthopaedic spine surgeon (CD’A). The threshold used to define scoliosis was a Cobb angle ≥ 20°. 25 Boys who did not receive spine surgery were only included in the scoliosis analysis if they had achieved 16 years of age.

Statistical analysis was performed using SPSS (IBM SPSS Statistics v. 26, Armonk, New York, USA). Two-way repeated measure analysis of variance (ANOVA) was used to determine if there were differences in height and weight velocity among the three groups pre- and post-CS treatment. Paired t-tests were used to determine whether height and weight velocities changed within a group, pre- to post-steroid initiation. One-way ANOVAs were used to determine if there were differences among the three groups for age at LOA, age when scoliosis was diagnosed and age at spinal surgery. Scheffé post hoc tests were used to identify where group differences occurred. Kruskal–Wallis was used to determine whether the incidence of scoliosis differed between groups. Pearson product moment correlation coefficients (r) were used to assess the relationship between total time on steroids, age at the initiation of steroids, the age of LOA, age when scoliosis was diagnosed and age at spinal surgery. Significance was set at p < 0.05.

Results

In all, 142 charts were reviewed for this study. Of these, 41 were excluded as boys did not meet the age requirement or have sufficient data to be included in the analysis. In total, 101 boys met the inclusion and exclusion criteria and were included in the analysis, although not every patient had all data points and thus the number of subjects included for each data point is included in the tables. There were 32 boys in the naïve group. From those that met the criteria, 69 boys were prescribed steroids, and of those, 37 (54%) reported that they were on a SOC dose. The LD group consisted of 32 boys (46%) who were on a suboptimal dose for all or part of the time, or after initially taking medication discontinued the drug completely. Of the 32 boys who were in the LD group, half of them stated that they took a lower dose due to behavioural or weight gain issues. Other reasons included a dislike of the Cushingoïd appearance and pseudotumor cerebri in one patient.

Age at initiation of CS treatment

Most boys in the naïve group attended our clinic in the early period of the study before corticosteroids were routinely prescribed, or during a time when there was still scepticism regarding the risk–benefit ratio of corticosteroid; thereby they had significantly earlier dates of birth (1989) as compared to the average date of birth (1998)
of the boys prescribed steroids. While both groups were followed on average into their 19th year of life, the steroid group was followed for 11.6 years as opposed to 7.8 years for the steroid naïve group, since the follow-up in this group began at a later age. Boys treated in the earlier years of the study also started steroid treatment at a later age than those treated more recently (Fig. 1).

**Height and weight velocity**

Height and weight followed standard curves in all groups prior to initiation of CS therapy, indicating normal growth rates. Two-way repeated measure ANOVAs were conducted to evaluate the effect of CS therapy (group) and time (pre/post-CS initiation) on height and weight velocity. For height velocity, there was no significant main effect for CS group $F(1,63) = 3.749, p = 0.03$, indicating the rate of linear growth was significantly different among the groups, but there was no significant main effect for time $F(1,63) = 3.508, p = 0.07$. To determine where group differences occurred pairwise comparisons (Scheffé tests) were used. There was a significant difference in height velocity between boys in the steroid naïve group and boys in the SOC group ($p = 0.034$), with boys in the SOC group demonstrating a significantly slower rate of linear growth than the boys in the naïve group. Boys in the naïve group continued to show an increase in height velocity during following institution of CS, consistent with the pre-pubertal growth spurt, while boys in both treatment groups showed a decrease in the rate of linear growth (Fig. 2). To determine within group changes in height velocity pre and post the initiation of CS therapy, paired-samples t tests were used. No significant difference in height velocity was seen in the naïve group; however, both the LD ($p = 0.001$) and SOC ($p = 0.014$) groups

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**Fig. 2** Height velocity.

**Fig. 3** Weight velocity.
demonstrated a significant slowing of height velocity following the onset of CS therapy (Fig. 2).

The two-way repeated measure ANOVA for weight velocity revealed a significant main effect for time $F(1,65) = 12.189$, $p = 0.001$, indicating that the rate of weight gain was significant for the total group across time; however, there was no significant main effect for group $F(1,65) = 0.129$, $p = 0.879$, thus the rate of weight gain between the groups was not significantly different. The results of paired-samples t tests to determine within group changes in weight velocity pre and post the initiation of CS therapy revealed no significant change in the naïve group, while both the LD ($p = 0.007$) and the SOC ($p = 0.002$) groups demonstrated a significant increase in the rate of weight gain with the initiation of steroid therapy (Fig. 3).

**Loss of ambulation**

One-way ANOVA revealed there was no significant difference among the groups $F(2,89) = 2.65$, $p = 0.076$ for the age at which ambulation was lost (LOA), although there was a trend to longer ambulation in the SOC group (Table 1).

Although the number of patients taking Prednisone versus Deflazacort was too small to be statistically analysed, boys in the SOC group on Prednisone alone (n = 10) demonstrated LOA at 10.1 years, similar to the naïve group. Boys in the SOC group who started on Prednisone, but switched to Deflazacort (n = 13) had LOA one year later than the naïve group, and those in the SOC group exclusively on Deflazacort (n = 6) exhibited LOA 3.4 years later than the naïve group.

Age at the initiation of CS therapy was not associated with age at LOA; however, the length of time on steroids demonstrated a weak ($r = 0.311$), but significant ($p = 0.016$) correlation with age at LOA (Table 2), indicating that as the length of time on steroids increased the age at LOA increased (Fig. 4).

**Scoliosis**

The Kruskal–Wallis test showed that there was a statistically significant difference in the incidence of scoliosis (Cobb angle ≥ 20°), $X^2 = 7.368$, $p = 0.025$, among the treatment groups with a reduction of incidence in both treatment groups versus the naïve group (Table 3). One-way ANOVA revealed no significant difference in age at onset of scoliosis among the groups ($F(2,41) = 0.229$, $p = 0.79$). Age at onset of scoliosis was not correlated with

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**Table 1** Age at loss of ambulation (years)

| Group | N  | Age at LOA (m/sd) |
|-------|----|------------------|
| Naïve | 29 | 10.84 (1.87)     |
| LD    | 29 | 10.39 (2.07)     |
| SOC   | 32 | 11.66 (2.57)     |

**Table 2** Correlations coefficients

|                      | Age at LOA | Age onset scoliosis | Age at spinal surgery |
|----------------------|------------|---------------------|-----------------------|
| Age at initiation of steroids | $r = 0.143$ | $r = 0.009$ | $r = -0.244$ |
| Total time on steroids     | $r = 0.311$ | $r = 0.548$ | $r = 0.005$ |
| Age at LOA                 | $r = 0.445$ | $r = 0.286$ | $r = 0.003$ |

LOA, loss of ambulation

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Fig. 4 Length of steroid use and age at loss of ambulation.
age at the initiation of steroids; however, age at onset of scoliosis did demonstrate a moderate ($r = 0.445$) and significant ($p = 0.003$) relationship with the age at LOA (Table 2). Of the 99 patients on whom we have scoliosis data, 69% of the steroid naïve group developed scoliosis, 52% of boys who were on Prednisone only developed scoliosis, for boys who took a combination of Prednisone and Deflazacort, 62% developed scoliosis, while of the boys who were on Deflazacort only, 47% developed scoliosis. Due to the small number of boys in some groups, no statistical analysis of the data was performed.

**Discussion**

Although there are many studies documenting prolongation of walking in boys with DMD treated with CS, and to a lesser extent a reduction of the incidence of scoliosis, our goal was to determine whether the positive outcomes reported in the literature with regard to scoliosis prevention and LOA was seen in boys treated with CS in our multidisciplinary MDA clinic.

**Compliance with dosage recommendation**

Many of the single-centre studies published come from large regional or national clinics that attract patients from long distances for regular follow-up visits. In these clinics parents are likely to have a high level of commitment and be highly reliable and compliant with prescribed medication dosage for their affected boys, although no studies report medication compliance data. Only 54% of boys that were prescribed CS remained on the recommended SOC dosage. It is recognized that using the medical record to assess adherence to the recommended dose is only an estimate, however, typically, patients were asked at each visit what dosage they were taking. Patients may overstate their compliance, but rarely understate it, so the number of patients who were non-compliant is, if anything, an underestimate. Even in published studies where patients keep diaries of medication usage, data is not reliable. 31,32

While CS have been shown to have a beneficial effect for functional, musculoskeletal and cardiopulmonary aspects of DMD, they have also been documented to have several adverse side effects including weight gain, significant reduction in stature, osteoporosis leading to an increased incidence of vertebral compression (VCF) and long bone fractures, as well as delayed puberty.18,33 Behavioural and mood issues are also frequent side effects, and may be severe.34 These side effects, particularly the behaviours in which aggression and depression predominate, may lead the parents and prescribing clinicians to choose to use a suboptimal dose, or discontinue CS use completely. Although it was strongly encouraged that boys remain on the SOC dose of CS, the effect these behaviours had on the psychosocial well-being of the boys and their families was recognized. If financially feasible, switching to Deflazacort was recommended if Prednisone was not well tolerated. If this was not financially feasible, taking a reduced dosage of Prednisone, or taking it at bedtime, was recommended. In several cases parents reported behaviour and mood dramatically improved after switching to Deflazacort, and our impression was that compliance with medication was improved when Deflazacort was used. Patients were maintained on daily administration, and rarely recommended other dosage schedules. When behaviour and mood changes became intolerable to patients and families, it was deemed inappropriate to adamantly demand that medication be maintained. Although psychological consultation was encouraged, and some patients were on psychotropic drugs, it was not possible to assess the efficacy of these interventions.

**Effects on linear growth and weight gain**

An expected CS effect is decreased height growth, and accelerated weight gain, which in many boys is quite dramatic, and once it is seen, is usually sustained as long as they are on their medication. This decrease in height velocity was used to confirm patients were taking their medication. Patients on both SOC and LD demonstrated a decreased height velocity and increased weight velocity following the initiation of CS. In many individual cases an almost complete cessation of linear growth was seen. The combination of decreased linear growth and weight gain indicate that CS are being taken, although these responses are not indicators of dosage levels, as threshold effects have not been defined. Although the mean rate of linear growth (height velocity) in the boys who took SOC dosage was reduced, there were individual patients in whom the growth rate was unchanged, but other CS side effects such as Cushingoid facies were exhibited.

It is concluded that if there is a robust change in the rate of linear growth, this is positive evidence that the patient is taking some CS, although not necessarily the full recommended dose; however, if height velocity is unaltered non-compliance can not be assumed. Similarly, not all boys showed increased weight gain, and it seemed that those who tended to be thin before starting CS had a higher likelihood of not showing the dramatic weight gain seen in others. Furthermore, since many boys ceased

| Table 3 Scoliosis |
|-------------------|
| Group  | N | Percentage scoliosis (m/sd) | Age at spinal surgery (m/sd) |
|--------|---|-----------------------------|-----------------------------|
| Naive  | 29 | 69%                         | 13.3 (2.1)                  |
| LD     | 32 | 41%                         | 15.0 (3.2)                  |
| SOC    | 36 | 47%                         | 13.4 (0.72)                 |
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Growing while gaining weight, a more reliable measure would be to use the body mass index, which, for regulatory reasons, it was not possible to obtain retroactively.

It appears that the effects of CS may not influence all expected outcomes to the same degree in individual patients. Patients may experience decreased height growth, Cushingoid facies, and relative preservation of muscle strength, and still develop scoliosis (Fig. 5).

Ambulation

Although LOA was not significantly different between groups in this study there was a trend towards a later LOA in the SOC group. Most published studies show a two-year prolongation of ambulation with CS treatment; however, this study did not see an effect of this magnitude. Although the numbers were too small for statistical analysis, there was an advantage on LOA for those taking Deflazacort versus Prednisone, an effect also seen in other studies.18,35

Hispanic and South Asian patients have been shown to lose ambulation significantly earlier than Caucasian boys receiving CS, and although the ethnic distribution of the patients is unavailable, there are a number of Hispanic boys and their genetic background may reduce the protective effect of CS for ambulation.36

Objective measures, such as the ten-metre walk, were not used to assess LOA in this study; chart notes were used to determine when LOA occurred. Since loss of the ability to ambulate is such a significant milestone, and ambulatory status was observed at each visit, utilization of chart notes to determine LOA is reasonably reliable. Age at initiation of CS treatment was not associated with age at LOA, which has been shown to influence this parameter;5 however, the length of time on CS was correlated with a later age at LOA. This finding may be inevitable, since the longer a subject walks, the longer they will have been on CS prior to LOA. Although not significant, the boys in our study on a suboptimal dose trended to an earlier LOA than the naïve group, possibly because this group experienced greater weight gain, while not deriving the beneficial effects of CS for maintenance of muscle strength for walking.

Scoliosis

There was an incidence of scoliosis of 69% in the untreated boys, 47% in those who were on the full SOC dose and 41% in the LD group. This difference, although significant, was not as robust as was reported in the studies from Toronto (Table 4), which reported that the incidence of scoliosis was reduced dramatically from 90% in the untreated boys to 10% to 20% in those treated with Deflazacort.8,25 In this study, the patients in the SOC group were taking Deflazacort, Prednisone or may have transitioned to Deflazacort following Prednisone use, which may have

Fig. 5 This patient walked until the age of 13.5 years. (a) Growth chart showing almost complete cessation of linear growth following administration of Deflazacort at 30 mg/day. (b) Radiograph of same boy at age 15 showing a 37.2° scoliosis, which was first ascertained six months earlier when it was 28°. His FVC at this time was 60% of predicted.

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Table 4  Studies reporting influence of Deflazacort on development of scoliosis

| Study (ref no.) | Drug       | No. patients | Scoliosis incidence/naïve | Scoliosis incidence treated |
|---------------|------------|--------------|---------------------------|----------------------------|
| Alman Toronto4 | Deflazacort | 74           | 30/34 – 90%                | 4/40 – 10%                  |
|               |            |              | Age 18 min.               | Age 18 min.                |
|               |            |              | 22/24 – 92%               | 6/30 – 20%                 |
|               |            |              | Mean age 22 (range 20 years–26 years) | Mean age 22 (range 20 years–26 years) |
|               |            |              | 28/42 had scoliosis with mean 46° | None <18°                  |
|               |            |              |                           | Mean age 13.1              |
|               |            |              |                           | 1/49 ‘required’ scoliosis surgery |
| Lebel Toronto35 | Deflazacort | 54           |                           |                           |
| Houde Montreal22 | Deflazacort | 79           |                           |                           |
| Singh Vancouver BC36 | Deflazacort | 37           |                           |                           |
| Wong Cincinnati24 | 90% Deflazacort, 10% Prednisone | 6/38 (16%) had scoliosis < 20% | Age 13 years to 16 years |

There are additional studies in which the assessment of scoliosis is included; however, they all have significant deficiencies including lack of information regarding how closely surveillance is done, inclusion of skeletally immature patients in the analysis, and the use of incidence of spinal surgery as a measure for scoliosis, which is not appropriate.23,24,29,39

Surgery is not an outcome measure, although the criteria for performing the surgery is an appropriate measure. In addition to the surgical decision making having a subjective component, there are also patients who meet the criteria and refuse surgery. It is disappointing that these centres carefully followed many measures of strength and function, but the assessment of scoliosis was not as carefully done. In order to reliably assess the incidence of scoliosis, boys must have consistent screening examination by a knowledgeable clinician to include an Adams forward bend test, which can be done on a seated patient. Once spinal asymmetry is detected, spinal radiographs should be taken at six to 12-month intervals, either standing in patients with stable standing ability, or sitting in those who are unable to stand. Since scoliosis develops as long as boys are skeletally immature, and puberty is delayed in those on CS, in order to determine the true incidence of scoliosis the population must only include those reaching at least age 16. Inclusion of younger boys will underestimate the incidence of scoliosis in the population. In many clinics the orthopaedist is a consultant, and not a primary member of the clinic team, which may account for deficiencies in this area. Therefore, all clinics are urged to include a knowledgeable orthopaedist as a full member of the clinical team, and be included in the development of outcome studies. Furthermore all orthopaedists who are involved in Muscular Dystrophy Association (MDA) clinics should assume this active role in the clinical programme as well as in development and implementation of clinical research studies (Fig. 6).

In our study, a 16-year age minimum was used for inclusion in the scoliosis analyses, and found a significant effect of corticosteroid on the incidence of scoliosis in boys taking CS. The influence of CS on scoliosis was not as robust...
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as found in some other studies, which may, in part, be
due to the fact that the incidence of scoliosis in our naïve
group was 69%, which was lower than the 90% found in
most series.\textsuperscript{6,21,24} If our naïve group had an incidence of
90% scoliosis, then the effect of CS would be even more
evident. It is speculated that the presence of modifying
genes that can contribute to differences in disease pro-
gression and impart a resistance to the effect of CS may
have contributed to the lack of more robust group differ-
ences in scoliosis.\textsuperscript{36} Hispanic and South Asian patients have
been shown to lose ambulation significantly earlier than
Caucasian boys receiving CS. A number of Hispanic boys
are seen in our clinic and their genetic background may
reduce the protective effect of CS for scoliosis in addition
to the influence on ambulation.\textsuperscript{36} A skewed distribution of
these, and possibly other, gene variations in either group
could have a significant effect on the outcomes of patients
when the groups are relatively small. The assessment of
gene modifications in our patients was not possible, as
this gene analysis was not available to us.\textsuperscript{40,41}

An issue not fully addressed in this study due to insuf-
ficient numbers was the efficacy of Deflazacort \textit{versus}
Prednisone in prevention of scoliosis, which may have dif-
ferential influence on this parameter. Scoliosis may have
been better controlled by Deflazacort, where the incidene
was 47%, as compared to 69% in the steroid naïve group
and 56% in boys who were taking Prednisone only. The
studies reporting the best outcome regarding protection
against scoliosis used Deflazacort exclusively.\textsuperscript{8,22,25,38} In
our study, a later LOA was seen in patients taking Deflazacort
in comparison to those on Prednisone alone. During much
of the time of our study, Deflazacort was preferred for its
perceived behavioural and weight gain benefits, but it had
to be obtained by our families from non-USA pharmacies
at a greater cost than Prednisone, so many patients were
unable to afford it and stayed on Prednisone, sometimes at
suboptimal dosage due to side effects. Deflazacort is now
Food and Drug Administration approved, and available
in the US, but the cost has jumped from around $100/
onth to $5,800/month, and most third-party payers have
stringent requirements for coverage of this medication. It
is not clear whether Deflazacort is intrinsically more effica-
cious than Prednisone for prevention of scoliosis and LOA
based on the present evidence or whether patients toler-
ate it better and thereby take the full recommended dose.
Due to the small numbers in each subgroup, statistical
analysis was not possible.

A final factor that could potentially influence the impact
of corticosteroid on length of ambulation as well as devel-
opment of scoliosis may be the age at which corticoste-
roid treatment is initiated. This ranged in reported studies
from 5.1 years\textsuperscript{42} to 7.7 years,\textsuperscript{1} and in our study, was 8.8
years, and trended earlier as more experience was gained
with steroid use. There was no correlation in this study
between age at initiation of steroid and LOA or scoliosis
prevention, similar to the recently published study of Kim
et al.\textsuperscript{43}

Although Wong et al advocate early initiation of steroid
treatment beginning at age four,\textsuperscript{42} this opinion is not uni-
versally shared. Initiation of steroid at a younger age will
result in an even more marked potential loss of height
growth in children, and a greater risk of VCF. Singh et al
found the length of time on CS correlated with greater loss
of overall height and higher incidence of VCF, which were
present in 91% of patients in their series by age 15,\textsuperscript{38} as
well as other metabolic effects. However, if starting at a

\begin{itemize}
\item Regular systematic clinical screening
\item Radiographs at regular intervals once scoliosis is clinically diagnosed
\item Type of medication and dosage defined
\item Cobb angle to diagnose scoliosis >20°
\item Surgery alone cannot be used as an outcome measure
  \begin{itemize}
  \item This does not account for patients who meet the criteria for surgery, but
    either refuse, or are at too high a risk to be considered.
  \item Criteria on which surgery is based (i.e. Cobb angle is a relevant and valid
    measure)
  \end{itemize}
\item Follow-up until at least age 16 minimum, since curves may not develop until this
  age in DMD, particularly with CS treatment that delays puberty
\item Consistent drug regimen
  \begin{itemize}
  \item Adequate dosage and duration of treatment
  \item Assessment of compliance
  \end{itemize}
\item Concurrent comparison group advisable
  \begin{itemize}
  \item Randomization is not feasible
  \end{itemize}
\end{itemize}

\textbf{Fig. 6} Recommendations for studies of scoliosis in patients with Duchenne muscular dystrophy.
younger age were shown to maximize the positive effects of corticosteroid, consideration should be given to earlier administration of drug after fully informing parents of both the potential risks as well as the potential benefits. Kim et al. found in a group of 477 boys with DMD that those receiving short-term CS (0.25 years to 3 years) had an earlier LOA by 0.8 years, while those who were on CS long term (>3 years) had an increased LOA by 2 years; however, there was no correlation with age at onset of drug treatment in this study. Similarly, there was a relationship between LOA and length of time on CS, but not age of onset of CS therapy. Some clinicians report that the corticosteroid side effects, although significant are ‘manageable’. In this retrospective review, many, although not all, patients on Prednisone did have side effects, which in many cases are very troubling to patients and family. This includes changes in mood and behaviour, and many parents report an abrupt change in behaviour with much more aggressive behaviour towards siblings and classmates in patients who are taking Prednisone, which is ameliorated when the medication is discontinued or they are switched to Deflazacort. In addition, many patients experience dramatic weight gain. It does seem that these complications are reduced in patients where Deflazacort is used.

Conclusion

It is clear that CS can provide significant benefits to boys with DMD, but it is not a ‘cure’ and there are also significant side effects. Parents should be counselled that ambulation may be prolonged, and the risk of scoliosis will be reduced, but not necessarily to the degree seen in those studies with the best outcomes, and not for all boys with DMD. Positive benefits may be maximized by complying with the prescribed dose, and possibly use of Deflazacort. However, dosage in some cases must be balanced by the severity of the side effects, particularly behaviour, which can affect not only the patient’s well-being, but also that of the family. Although there is not strong evidence in the literature for the efficacy of Prednisone or Prednisolone for prevention of scoliosis, this does not mean that such an effect is absent. Newer medications currently in clinical trials, such as Edasalonexent (Catabasis Pharmaceuticals, Boston, Massachusetts, USA), may eliminate some of the side effects associated with CS while providing significant benefit, and hopefully the data from their study will include adequate assessment of scoliosis. However, it is clear that corticosteroid has extended the functional life span of boys with DMD, and at this point in time remains an essential base of our medical treatment programme.

Finally, it is recommended that knowledgeable orthopaedists be active members of MDA clinics and be full partners in the clinical and research programmes therein.
CORTICOSTEROIDS FOR PREVENTION OF SCOLIOSIS IN DMD

1. Barlow J, Wilkins KE, Gibson DA. The patterns of spinal deformity in Duchenne muscular dystrophy. J Bone Joint Surg [Am] 1976;58:24-52.

2. Passamano L, Taglia A, Palladino A, et al. Improvement of survival in Duchenne Muscular Dystrophy: retrospective analysis of 835 patients. Acta Myol 2012;31:211-25.

3. DeSilva S, Drachman DB, Mellits D, Kunc RW. Prednisone treatment in Duchenne muscular dystrophy. Long-term benefit. Arch Neurol 1987;44:818-822.

4. Mendell JR, Moxley RT, Griggs RC, et al. Randomized, double-blind six-month trial of prednisone in Duchenne’s muscular dystrophy. N Engl J Med 1989;320:1592-1597.

5. Biggar WD, Gingras M, Fehlings DL, Harris VA, Steele CA. Deflazacort treatment of Duchenne muscular dystrophy. J Pediatr 2001;138:45-50.

6. Birnkrant DJ, Bushby K, Bann CM, et al; DMD Care Considerations Working Group. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and neuromuscular, rehabilitation, endocrine, and gastrointestinal and nutritional management. Lancet Neurol 2018;17:251-267.

7. Gloss D, Moxley RT III, Ashwal S, Oskouei M. Practice guideline update summary: Corticosteroid treatment of Duchenne muscular dystrophy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology 2016;86:465-472.

8. Angelini C, Pegoraro E, Turella E, Intino MT, Pini A, Costa C. Deflazacort in Duchenne dystrophy: study of long-term effect. Muscle Nerve 1994;17:386-391.

9. Barber BJ, Andrews JG, Lu Z, et al. Oral corticosteroids and onset of cardiomyopathy in Duchenne muscular dystrophy. J Pediatr 2013;163:1080-1084.

10. Bello L, Gordish-Dressman H, Morgenroth LP, et al; CINRG Investigators. Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study. Neurology 2015;85:1048-1055.

11. Finder JDA. A 2009 perspective on the 2004 American Thoracic Society statement, “respiratory care of the patient with Duchenne muscular dystrophy”. Pediatrics 2009;123:5239-5241.

12. Griggs RC, Moxley RT III, Mendell JR, et al; Clinical Investigation of Duchenne Dystrophy Group. Prednisone in Duchenne dystrophy. A randomized, controlled trial defining the time course and dose response. Arch Neurol 1997;48:383-388.

13. Hawker GA, Ridout R, Harris VA, Chase CC, Fielding LJ, Biggar WD. Alendronate in the treatment of low bone mass in steroid-treated boys with Duchenne’s muscular dystrophy. Arch Phys Med Rehabil 2005;86:284-288.

14. Honig SJ, Fournier A, et al. Deflazacort use in Duchenne muscular dystrophy: an 8-year follow-up. Pediatr Neurol 2008;39:200-206.

15. King WM, Rutten CUTTER R, Nagaraja HN, et al. Orthopedic outcomes of long-term daily corticosteroid treatment in Duchenne muscular dystrophy. Neurology 2007;68:1607-1613.

16. Koeks Z, Bladen CL, Salgado D, et al. Clinical outcomes in Duchenne muscular dystrophy: a study of 5345 patients from the TREAT-NMD DMD global database. J Neuromuscul Dis 2014;4:293-306.

17. Lebel DE, Corston JA, McAdam LC, Biggar WD, Alman BA. Glucocorticoid treatment for the prevention of scoliosis in children with Duchenne muscular dystrophy: long-term follow-up. J Bone Joint Surg [Am] 2015;97:1057-1061.

18. Raudenbush BL, Thirukumaran CP, Li Y, Sanders JO, Rubery PT, Mesfin A. Impact of a comparative study on the management of scoliosis in Duchenne muscular dystrophy: are corticosteroids decreasing the rate of scoliosis surgery in the United States? Spine (Phila Pa 1976) 2016;41:E930-E938.

19. Ricotti V, Rudout DA, Scott E, et al; NorthStar Clinical Network. Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy. J Neurol Neurosurg Psychiatry 2015;84:698-705.

20. Wagner KR, Lechtzin N, Judge DP. Current treatment of adult Duchenne muscular dystrophy. Biochim Biophys Acta 2007;1772:229-237.

21. Dooley JM, Gordon KE, MacSween JM. Impact of steroids on surgical experiences of patients with Duchenne muscular dystrophy. Pediatr Neurol 2010;43:173-176.

22. Singal AG, Higgins PD, Waljee AK. A primer on effectiveness and efficacy trials. Clin Transl Gastroenterol 2014;5:645.

23. Conn VS, Ruppar TM. Medication adherence outcomes of 771 intervention trials: systematic review and meta-analysis. Prev Med 2017;99:269-276.

24. Ryan TP, Morrison RD, Sutherland JJ, et al. Medication adherence, medical record accuracy, and medication exposure in real-world patients using comprehensive medication monitoring. PLoS One 2017;12:e0185471.

25. Sussman M. Duchenne muscular dystrophy. J Am Acad Orthop Surg 2002;10:138-151.

26. Sienko S, Buckon C, Fowler E, et al. Prednisone and Deflazacort in Duchenne muscular dystrophy: do they play a different role in child behavior and perceived quality of life? PLoS One 2016;8:e015471.

27. Shieh BP, McIntosh J, Jin F, et al; The ACT DMD Study Group. Deflazacort versus prednisone/prednisolone for maintaining motor function and delaying loss of ambulation: A post HOC analysis from the ACT DMD trial. Muscle Nerve 2018;58:639-645.

28. Bello L, Kesari A, Gordish-Dressman H, et al; Cooperative International Neuromuscular Research Group Investigators. Genetic modifiers of ambulation in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study. Ann Neurol 2015;77:684-696.
37. **Harvey A, Baker L, Williams K.** Non-surgical prevention and management of scoliosis for children with Duchenne muscular dystrophy: what is the evidence? J Paediatr Child Health 2014;50:E3-E9.

38. **Singh A, Schaeffer EK, Reilly CW.** Vertebral fractures in Duchenne muscular dystrophy patients managed with Deflazacort. J Pediatr Orthop 2018;38:320-324.

39. **Balaban B, Matthews DJ, Clayton GH, Carry T.** Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: long-term effect. Am J Phys Med Rehabil 2005;84:843-850.

40. **Pegoraro E, Hoffman EP, Piva L, et al; Cooperative International Neuromuscular Research Group.** SPP1 genotype is a determinant of disease severity in Duchenne muscular dystrophy. Neurology 2011;76:219-226.

41. **Flanigan KM, Ceco E, Lamar KM, et al; United Dystrophinopathy Project.** LBP4 genotype predicts age of ambulatory loss in Duchenne muscular dystrophy. Ann Neurol 2013;73:481-488.

42. **Wong SC, Straub V, Ward LM, Quinlivan R; 236th ENMC workshop participants.** 236th ENMC International Workshop Bone protective therapy in Duchenne muscular dystrophy: determining the feasibility and standards of clinical trials Hoofddorp, The Netherlands, 1-3 June 2018. Neuromuscul Disord 2019;29:251-259.

43. **Kim S, Zhu Y, Romitti PA, et al; MD STARnet.** Associations between timing of corticosteroid treatment initiation and clinical outcomes in Duchenne muscular dystrophy. Neuromuscul Disord 2017;27:730-737.