RESEARCH PAPER

Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy

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ABSTRACT

Objective To assess the current use of glucocorticoids (GCs) in Duchenne muscular dystrophy in the UK, and compare the benefits and the adverse events of daily versus intermittent prednisolone regimens.

Design A prospective longitudinal observational study across 17 neuromuscular centres in the UK of 360 boys aged 3–15 years with confirmed Duchenne muscular dystrophy who were treated with daily or intermittent (10 days on/10 days off) prednisolone for a mean duration of treatment of 4 years.

Results The median loss of ambulation was 12 years in intermittent and 14.5 years in daily treatment; the HR for intermittent treatment was 1.57 (95% CI 0.87 to 2.82). A fitted multilevel model comparing the intermittent and daily regiments for the NorthStar Ambulatory Assessment demonstrated a divergence after 7 years of age, with boys on an intermittent regimen declining faster (p<0.001). Moderate to severe side effects were more commonly reported and observed in the daily regimen, including Cushingoid features, adverse behavioural events and hypertension. Body mass index mean z score was higher in the daily regimen (1.99, 95% CI 1.79 to 2.19) than in the intermittent regimen (1.51, 95% CI 1.27 to 1.75). Height restriction was more severe in the daily regimen (mean z score −1.77, 95% CI −1.79 to −2.19) than in the intermittent regimen (mean z score −0.70, 95% CI −0.90 to −0.49).

Conclusions Our study provides a framework for providing information to patients with Duchenne muscular dystrophy and their families when introducing GC therapy. The study also highlights the importance of collecting longitudinal natural history data on patients treated according to standardised protocols, and clearly identifies the benefits and the side-effect profile of two treatment regimens, which will help with informed choices and implementation of targeted surveillance.

INTRODUCTION

Duchenne muscular dystrophy (DMD) is a progressive X-linked neuromuscular disease, affecting 1 in 3600 live male births.[1 2] It classically presents in the first years of life with proximal muscle weakness, progressing to loss of ambulation, historically by 9.5 years (range 6–12) if untreated.[3] In the second decade respiratory, cardiac and orthopaedic complications arise, leading to premature death.[3]

Glucocorticoids (GCs) are the only pharmacological intervention to slow progression of weakness, reduce development of scoliosis and delay respiratory insufficiency.[4–6] The precise mechanism is unknown, but it has been hypothesised that GCs have anti-inflammatory and immunosuppressive actions, promote myoblast proliferation and reduce muscle necrosis.[7] In mdx dystrophic mice, RNA profiling studies identified overexpression of metabolism, proteolysis and structural protein genes, and differential expression of calcium metabolism genes.[7]

Few large-scale randomised clinical trials have been published on GCs in DMD.[8–11] GCs lead to early improvement in muscle strength and function. In the longer term, GCs slow decline of muscle function and prolong ambulation.[12] The most effective therapeutic strategy postulated is prednisolone/prednisone 0.75 mg/kg/day or the equivalent deflazacort (0.9 mg/kg/day).[4] Higher daily doses (1.5 mg/kg/day) were not shown to be more effective and lower doses (0.35 mg/kg/day) were less effective.[4 8] GC side effects include adverse behavioural changes, Cushingoid features, obesity, growth retardation, hypertension and bone demineralisation with increased risk of vertebral fractures.[4–6] To minimise the side effects, other regimens have been suggested. A widely used regimen in the UK is intermittent dosing, 10 days on/10 days off, which allows drug-free periods, possibly without losing overall benefit.[13] Recent short-term data showed that pulse administration of steroids had less detrimental effect compared with the daily regimen, but was less efficacious.[9]

GCs are recommended in the international standards of care guideline for DMD,[5 6] which has been accredited by the National Institute for Health and Clinical Excellence (NICE). The benefits of GCs are internationally acknowledged and confirmed by Cochrane systematic reviews, but uncertainties remain as to different regimen-associated tolerability, efficacy and long-term effects.[14] Treatment initiation is advised between 4 and 6 years, when motor skills begin to plateau.[5] Prednisolone is preferred because of its availability and cost; the choice of regimen is guided by the discussion between family and physician, and the anticipated tolerability of a specific regimen. Some boys are switched from daily to intermittent GCs or vice versa, for intolerable

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Table 1 Key medical and physiotherapy information recorded on the database

Baseline information	Medical information at follow-up	Outcome measures at follow-up
Demographic data	Date of starting GCs	Ambulation status and mobility aids
Genetic mutation*	Current dose and regimen of GCs	Age at loss of independent ambulation
Maternal carrier status*	Adverse behavioural changes	Respiratory status (FVC, FVC%)
Date of diagnosis	Gastrointestinal symptoms	Echocardiogram (LVFS%)
Features of the muscle biopsy†	Increased appetite	NorthStar Ambulatory Assessment score
Family and social history	History of infections	Time rising from the floor from lying
	Height and weight	Timed 10 m run
	Blood pressure	Manual muscle testing
	Cushingoid features	Joint range
	Bone density measurements	Spinal posture
	Long bone fractures and vertebral fractures	
	Cataracts	
	Hirsutism	
	Delayed puberty	
	Other therapeutic interventions	
	Adjustment in GC dose/regimen	

*Genetic diagnosis and maternal carrier status confirmed by a state-of-the-art DNA diagnostic technique covering all Duchenne muscular dystrophy gene exons.
†Dystrophin expression observed on muscle biopsy by immunohistochemistry with monoclonal antibodies dys1, dys2, dys3 (ie, complete absence, traces).
FVC%, forced vital capacity percentage; GC, glucocorticoid corticosteroids; LVSF%, left ventricular shortening fraction percentage.

side effects, deterioration of function and reappraisal of the risk–benefit ratio. Deflazacort has shown less associated weight gain but an increased risk of cataracts.[15]

The NorthStar clinical network for paediatric neuromuscular disease (NSCN) was established in the UK at the end of 2003, with the objective of optimising the care and acquiring longitudinal natural history data on boys with DMD treated and assessed according to a specified standardised protocol.[5 6] There are 17 participating specialist paediatric neuromuscular centres. A secure web-based database has been used for data collection since 2006. Prospective data are uniformly and systematically collected across centres, facilitating national audits.

We analysed data collected through the NCSN from January 2004 to September 2011. We focused on clinical outcomes from different GC regimens and analysed outcome measures and side effects in the largest steroid-treated cohort of boys with DMD studied to date.

METHODS

The NorthStar database

The NorthStar database collects clinical information on boys with DMD with an out-of-frame mutation in the DMD gene, confirmed by DNA diagnostic technique covering all DMD gene exons, including but not limited to multiplex ligation-dependent probe amplification. When DMD deletions or duplications were not identified, all 79 exons and the adjacent introns were analysed through PCR amplification and direct sequencing, although the search for point mutation was not available uniformly throughout the UK. Mutations were classified according to the Leiden Muscular Dystrophy database.[16]

Boys with no confirmed mutation but absent dystrophin in muscle biopsy (<5% on immunohistochemistry) were also included in the database. Information was recorded with signed parent/guardian informed consent. The data were linked anonymised and each subject was assigned a unique NorthStar ID number. Physicians and physiotherapists completed standardised forms biannually. A national training programme was implemented to ensure standardisation of physiotherapy data collection across centres and a national coordinator assured standardised retraining across the network. Baseline information was recorded at registration (table 1). At each follow-up, medical and physiotherapy data were documented, including steroid regimen, side effects, outcome measures and a management plan (table 1).

Physiotherapy outcome measures

The NorthStar Ambulatory Assessment (NSAA) is a validated composite scale to measure function in ambulant boys with DMD.[17 18] This scale is widely used in the UK, internationally and in clinical trials[19–23] and has recently been confirmed by Rasch analysis to be psychometrically robust.[21] The assessment consists of 17 items (box 1), with three ordered response categories (maximum score 34). Items can be scored 2 (activity carried out normally with no obvious modification), 1 (goal

Box 1 The 17 items of the NorthStar Ambulatory Assessment

Stand
Walk
Stand up from chair
Stand on right leg
Stand on left leg
Climb box step—right leg
Climb box step—left leg
Descend box step—right leg
Descend box step—left leg
Gets to sitting
Rise from the floor
Lift head
Stand on heels
Jump
Hop—right leg
Hop—left leg
Run (10 m)

achieved independently with modified method) or 0 (task cannot be performed independently). Clear instructions are described in the data entry form. The scale is completed in 20 min and contains a number of timed tests: timed 10 m run test (10 mRT), timed rising from the floor from lying (Gowers' manoeuvre).

Side effects

Side effects recorded include objective evaluations carried out during clinical appointments (ie, weight, height, blood pressure, whole spine bone density measurements, vertebral fractures), and adverse events reported by the families/boys and logged by the physician as mild, moderate or severe (ie, first presentation or aggravation of behavioural problems, insomnia, abdominal pains, gastroesophageal reflux, increased appetite, history of infections) according to the instructions provided in the clinical forms, which were discussed and agreed at national consensus meetings organised at the inception of the network.

Patient population

At the time of data analysis in September 2011, 500 patients were registered on the NorthStar database. Prospectively collected longitudinal data were available for 360 boys with DMD between 2004 and 2011 (figure 1, see web appendix 1) ranging in age from 3 to 17 years. Longitudinal data were available only for boys treated with GCs, who represent the large majority of boys with DMD in the age range studied (table 2A). GC therapy is systematically offered and only exceptionally refused by parents. We classified boys according to the GC regimen: daily prednisolone, intermittent prednisolone 10 days on/10 days off, prednisolone on alternate days, and deflazacort treatment. Some boys changed regimen of GC between daily and intermittent or vice versa (switchers). All patients included were treated according to the integrated multidisciplinary standard of care[5 6] and assessed by specialised neuromuscular physiotherapists.

STATISTICAL METHODS

We described the general patient characteristics for each GC regimen. As this is an observational study and some boys switched regimens throughout the course of their treatment, comparisons between regimens were analysed in three ways: as per initial treatment, daily versus intermittent; by majority of treatment, daily versus intermittent, as defined by the overall majority of time treated with one regimen (≥60% of time); by removing switchers. The results for these three approaches were very similar for all analyses; therefore, we have presented the final results for the most clinically relevant 'majority of treatment' (daily or intermittent). Switchers were too heterogeneous to be grouped as one cohort of patients for the purposes of the analysis.

For the time to loss of ambulation (LOA) a Cox regression model was used to compare the effect of daily versus intermittent. An adjustment was made for random centre effects and hence the HR is presented along with a 95% CI, derived using

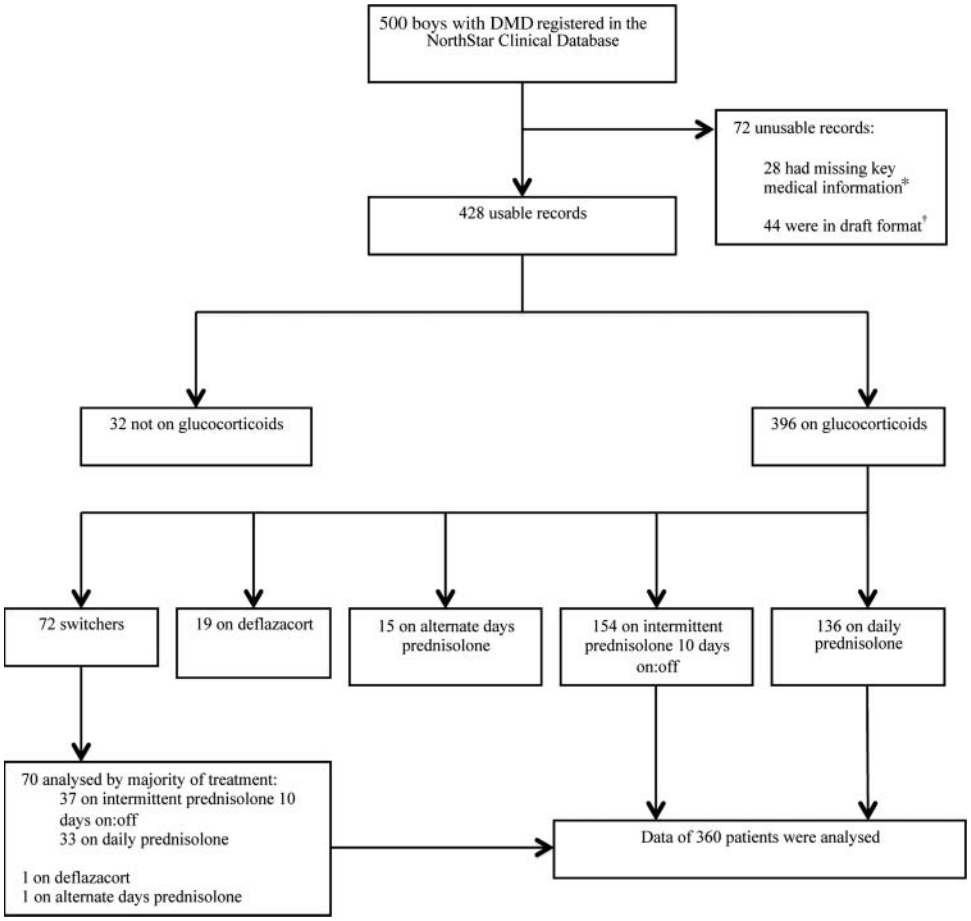

Figure 1 Flow of patients from registration in the database to enrolment in the study. *Data with missing key medical information refers to essential data required for statistical analysis (eg, dose of glucocorticoids, date of birth of the patient, date of assessment). †Assessments saved in draft format were not confirmed, therefore excluded from the analysis. DMD, Duchenne muscular dystrophy.

Table 2 General characteristics of patients

	Age of diagnosis (years)	Age of starting GCs (years)	Duration of treatment (years)	Dose of GCs (mg/kg/day)	Duration of follow-up (years)
A					
IP (n=154)	4.4 (0.3–9.4)	6.5 (4.2–9.6)	3.6 (0.5–8.5)	0.6 (0.3–0.8)	2.5 (0.2–5.4)
DP (n=136)	4.3 (0.3–9.4)	6.2 (4.2–9.8)	4.3 (0.5–7.5)	0.5 (0.3–0.8)	2.7 (0.3–7.8)
SW (n=72)	4.2 (0.2–8.6)	6.3 (3.4–9.2)	4.1 (0.7–7.8)	0.6 (0.3–0.8)	3.2 (0.4–6.9)
DFZ (n=19)	5.5 (0.5–8.7)	7.0 (5.2–9.3)	4.4 (0.6–7.9)	0.6 (0.4–0.9)	2.8 (0.6–7.0)
AD (n=15)	4.4 (1.3–8.2)	6.3 (4.4–9.0)	5.0 (2.4–7.5)	0.6 (0.3–0.8)	2.0 (0.2–3.9)
Not on GCs (n=32)	3.3 (0.9–6.9)	–	–	–	–
		IP	**DP**	**DFZ**	**AD**
B					
Starting regimen		57	12	2	1
Majority of treatment		37	33	1	1
Age of switching regimen (years), mean (range)		8.4 (5.6–12)	8.5 (7.3–9.3)	–	–

(A) Summary of patients' characteristics presented as mean (range) (n=428): age of diagnosis, age of starting steroids, duration of treatment, dose of steroids during the whole duration of treatment, and duration of follow-up since registration on the database. (B) Switchers (n=72): in the analysis, 70 switchers were included as per majority of treatment for intermittent and daily regimens.
AD, prednisolone on alternate days; DFZ, deflazacort; DP, daily prednisolone; GC, glucocorticoid corticosteroids; IP, intermittent prednisolone 10 days on/10 days off; SW, switcher.

robust standard errors. For the main longitudinal functional outcome measure NSAA score, a running line smoother was used to inspect the data graphically. This revealed a definite change in the relationship after about age 7, which was in line with what was observed clinically and reported before.[22] A piecewise linear spline with a single knot (changing point) at age 7 was used to allow for this effect. The spline was incorporated into a two-level multilevel model with the random effect of the patient nested within the random centre. This allowed comparison of the longitudinal effect of age between daily and intermittent regimens, before and after age 7 years, by fitting two interaction terms for age and regimen. We fitted a similar model for 10 mRT and the timing for the Gowers' manoeuvre; as these data were skewed, a log transformation was used. The longitudinal models were adjusted for the length of time on steroids prior to entry to the database. Additionally, we hypothesised that body mass index (BMI) may be related to outcome and therefore explored the models adjusting for BMI z score. As BMI data were unavailable for some observations (13%) we used multiple imputation with the method of chained equation to generate five imputed datasets, assuming the data were missing at random.[24] Estimates obtained from the multiple imputations were pooled to obtain a single set of results.

We compared the NSAA total score in boys who started GCs before age 5 versus after age 5 with a multilevel model adjusting for treatment. For respiratory and cardiac outcome measures a linear multilevel model was used to investigate the relationship of forced vital capacity percentage predicted (FVC%) and left ventricular shortening fraction percentage (LVSF%) respectively, with age and the interaction with treatment regimen.

Side-effect profiles reported by families and, if possible, measured during the consultation were compared as proportions by χ^2 analysis. The BMI was calculated from height and weight. Height, weight and BMI centiles for gender and age were derived against the British 1990 growth reference and converted to z scores (LMSGrowth calculator).[25] BMI z scores were described as means and 95% CIs. At the time of latest follow-up, differences between intermittent and daily BMI, height and weight z-score means were compared by regression analysis adjusted for length of time on steroids. Single measurements at last follow-up were used for patients on treatment for more than 1 year. BMI z-score means were compared for intermittent and daily regimens at baseline using a two-sample t test. Baseline included a pre-GC single measurement to a maximum of 3 months into treatment. Hypertension was defined as blood pressure >95th percentile.

For all tests, a p value of ≤ 0.05 was considered statistically significant. The statistics package Stata was used for the analysis.

RESULTS

Longitudinal data on 360 patients were included in the analysis (figure 1, see web appendix 1). Seventy-two percent of the patients registered in the database were recruited in the study. The mean age of starting GCs was 6.4 years (range 3.4–9.8) and the mean duration of treatment and follow-up was 3.9 years (range 0.5–8.5). Intermittent (n=154) and daily (n=136) regimens were the most common, used in 73% of boys on GCs; additionally 70 of 72 switchers were treated with daily or intermittent prednisolone (table 2B). The general characteristics of those on intermittent or daily regimens and switchers were similar in relation to age starting steroids, mean dose of GCs, duration of treatment, and duration of follow-up as NSCN-registered patients (table 2A). The mean dose of GCs was an overall group mean through the full period of treatment, which included dose adjustment in line with weight and tolerability. A total of 28 boys discontinued GCs.

Outcome measures

LOA was reported in 51/184 boys on the intermittent regimen and 39/168 of boys on the daily regimen (figure 2). Two boys were never ambulant and excluded from this part of the analysis; ambulation status was unknown for the remaining six. Median LOA was 12 years for the intermittent regimen and 14.5 years for the daily regimen. HR for the intermittent versus daily regimen was 1.57 (95% CI 0.87 to 2.82; p=0.13) and the mean age for LOA did not differ.

The longitudinal analysis of NSAA total score showed a difference in the relationship with age between the two regimens after 7 years of age (figure 3). The daily regimen showed the slowest decline, with the difference between the two regimens increasing by 1.58 units per year (95% CI 1.04 to 2.11; p<0.001). This result was consistent when adjusting

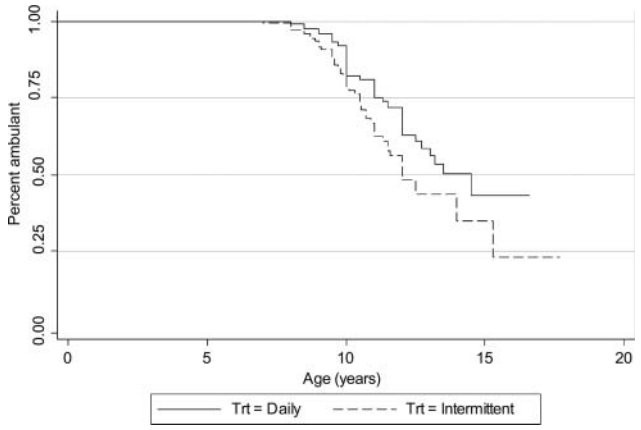

Figure 2 Kaplan–Meier survival estimates for loss of ambulation and Cox regression. Loss of ambulation was reported in 48/176 of boys on intermittent prednisolone and 36/165 of those on daily prednisolone. Median loss of ambulation: intermittent=12 years, daily=14.5 years. HR 1.57 (95% CI 0.87 to 2.82; p=0.13).

additionally for BMI z score. Adjusting the NSAA total score model for severe learning difficulties, we observed an overall difference in means (2.74 NSAA points, 95% CI 0.37 to 5.10; p=0.02), such that patients with learning difficulties performed worse. There was little change in the relationship with age between the intermittent and daily regimens (coefficient 1.36, 95% CI 0.79 to 1.94; p<0.001) compared with the model without learning difficulties. Comparison of the NSAA total score between patients who started GC who were over and under the age of 5 years, after adjusting for regimens, demonstrated an overall trend in favour of children who started early treatment (difference=3.04, 95% CI 0.15 to 6.23; p=0.06). For the 10 mRT outcome, there was evidence of a difference in the relationship over time between the two regimens after age 7 years, favouring the daily regimen. The difference increased by 6% per year on average (95% CI 3% to 9%; p<0.003). A similar trend was found for time rising from the floor (Gowers' manoeuvre), with a difference after age 7 of 6% per annum (95% CI 0% to 12%; p=0.06). After adjusting for BMI z score, the size of this effect decreased for both outcomes.

We also described the slope of decline for respiratory and cardiac function. Respiratory and cardiac outcomes did not differ between intermittent and daily regimens. The entire cohort (daily and intermittent together) was then analysed as one group. Within the age range of the cohort, mean values remained within the normal limits. However, there was a significant progressive decline in the FVC% by 2.2% per annum (p<0.001) after age 10 years; and in the LVSF% by 1% per annum (p<0.001) after 12 years.

Side effects

Side effects were summarised for intermittent and daily prednisolone, assigning switchers by 'majority of treatment' (table 3). Moderate and severe side effects were more frequently observed for the daily GC regimen. Statistically significant differences were found in the daily and intermittent regimens: Cushingoid features 33% and 15%, hyperactivity 23% and 15%, gastrointestinal symptoms 14% and 6%, and hypertension 22% and 5% respectively. Severe side effects alone were not significantly higher in the daily group. Baseline BMI did not differ between the intermittent and daily regimens (figure 4A), both groups gaining excessive weight (figure 4D). However, the mean height z score, adjusted for length of time on steroids, was significantly lower in the daily regimen, with a mean difference of 1.09 (95% CI 0.78 to 1.40; p<0.001) (figure 4C). The overall effect at latest follow-up was a significant increase from baseline in BMI in both regimens, but the daily regimen had a more severe effect than the intermittent regimen: mean difference 0.43 (95% CI 0.11 to 0.74); p<0.01 (figure 4B). Bone health was compromised in both regimens (table 3): bone mineral density z scores ≤−2.5 on dual-energy x-ray absorptiometry (DEXA) scan were observed in 5% of boys on the intermittent regimen and 8% of those on the daily regimen. Vertebral fractures were defined by the NSCN as vertebral wedging on lateral spine

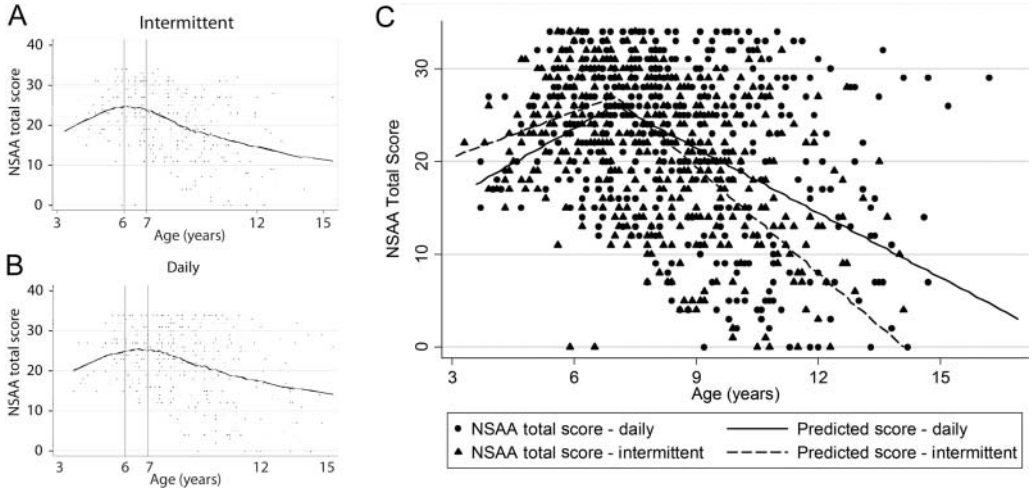

Figure 3 North Star Ambulatory Assessment (NSAA) total score for intermittent versus daily prednisolone. NSAA total score running line is smoother for intermittent (A) than for daily (B) prednisolone. NSAA decline began at 7 years in the daily group and at 6 years in the intermittent group. (C) A fitted multilevel model and interaction for the NSAA total score was calculated comparing intermittent and daily regimens. There were 862 episodes. There was a definite change in the relationship after 7 years of age: <7 years interaction coefficient −0.81 (95% CI 0.42 to 2.04; p=0.2); ≥7 years interaction coefficient −1.58 (95% CI 1.04 to 2.11; p<0.001). The score for the intermittent regimen deteriorates faster than for the daily regimen after 7 years of age. For each additional year, the difference in NSAA total score between the two regimens increases by 1.58 points.

Table 3 Moderate to severe side effects breakdown, χ^2 analysis (intermittent prednisolone n=191; daily prednisolone n=169)

Side effects	Intermittent, n (%)	Daily, n (%)	χ^2 p value
Temper tantrums	54 (28)	67 (40)	0.02*
Mood swings	56 (29)	64 (38)	0.08
Aggressiveness	41 (21)	49 (29)	0.09
Hyperactivity	29 (15)	39 (23)	0.05*
Emotional liability	23 (12)	32 (19)	0.06
Insomnia	8 (4)	19 (11)	0.01*
Cushingoid features	28 (15)	56 (33)	<0.01*
GI symptoms	12 (6)	23 (14)	0.01*
Increased appetite	73 (38)	78 (46)	0.1
Hypertension	10 (5)	38 (22)	<0.01*
Vertebral fractures	8 (4)	14 (8)	0.1
Long bone fractures	13 (7)	9 (5)	0.5
BMD z-score ≤ −2.5*	9 (5)	14 (8)	0.1
Cataracts	2 (1)	4 (2)	0.3
Hirsutism	19 (10)	24 (14)	0.2
Easy bruising	5 (3)	7 (4)	0.4

*BMD z score=lumbar spine.
BMD, bone mineral density; GI, gastrointestinal.

radiography[26] and were reported in 4% of boys on the intermittent regimen and 8% of those on the daily regimen.

DISCUSSION

We report the largest amount of prospectively collected multicentre longitudinal clinical data of ambulant boys with DMD treated with GCs according to internationally agreed standards of care. We describe the long-term efficacy and tolerability of intermittent versus daily prednisolone in 360 UK-treated boys with DMD, on treatment for a mean of 4 years. We included 191 boys on intermittent and 169 boys on daily prednisolone. Switchers (n=70) did not affect results and were analysed by 'majority of treatment' regimen.

Survival analysis of median LOA favoured daily treatment (14 years) with 2 years' advantage compared with the intermittent regimen (12 years). However, the HR was not statistically significant because the mean ages were not different. Boys with DMD lose ambulation by the end of the first decade if untreated,[3 27] however daily therapy has been shown to prolong ambulation beyond 13 years of age.[4 27] Additionally, the implementation of the international standards of care endorsed by the NSCN and NICE, through addressing the multisystem requirements of DMD, may also significantly contribute to prolongation of ambulation.

We demonstrated that the two regimens performed equally in respect of gain of function until 6 years of age. However, after age 7, the condition of boys on the intermittent regimen was found to decline more rapidly with an incremental difference (NSAA score 1.58 per annum). There was also a faster decline in the 10 mRT and Gowers' manoeuvre: 5% and 6% respectively per annum. Boys with severe learning difficulties performed worse on motor assessments, but this was not affected by steroid regimen. Our data indicate a clinically significant benefit in starting GCs early, fuelling the ongoing debate on how early treatment should be started.[28] A recent long-term case series of four boys with DMD treated between age 2 and 4 years reported prolonging ambulation beyond 16 years.[29] In our study, boys who began treatment before 5 years of age showed a trend towards slower functional decline.

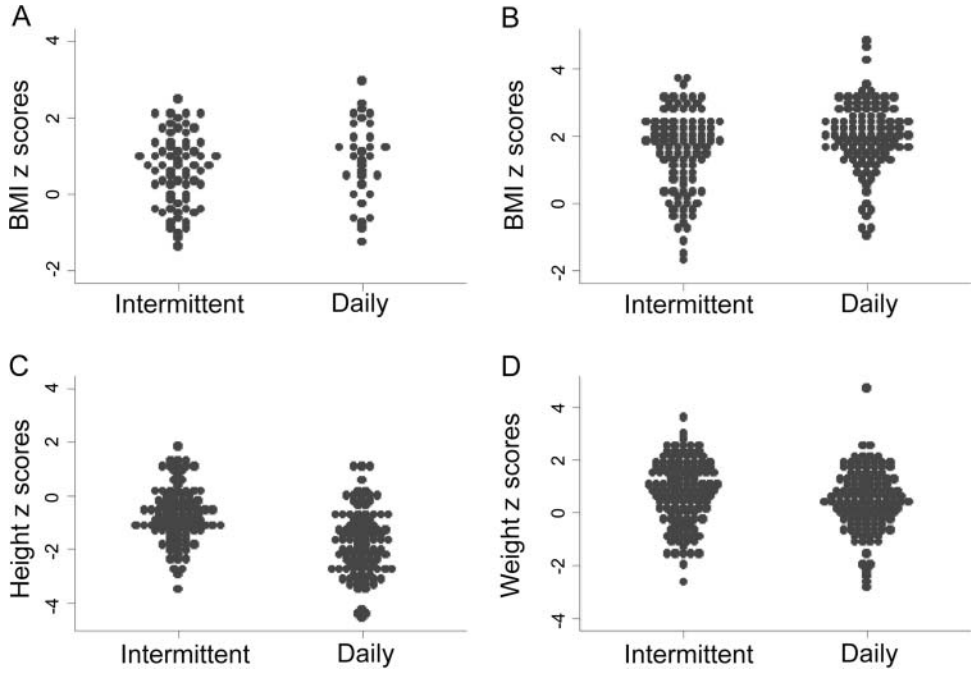

Figure 4 Body mass index (BMI), height and weight: intermittent versus daily prednisolone. (A) BMI z score (mean±95% CI) at baseline: there was no significant group difference between BMI. Intermittent (n=67) baseline mean z score 0.62 (95% CI 0.39 to 0.85), daily (n=32) baseline mean z score 0.88 (95% CI 0.50 to 1.27), p=0.2. (B) At maximum period of treatment* there was a group difference in BMI favouring intermittent (n=99) versus daily (n=102) treatment: intermittent BMI mean z score 1.51 (95% CI 1.27 to 1.75), daily 1.99 (95% CI 1.79 to 2.19), p=0.002. (C) Height restriction was significant in daily treatment group (n=104) but there was no group loss of height for the intermittent regimen (n=101): intermittent height mean z score −0.70 (95% CI −0.90 to −0.49), daily −1.77 (95% CI −2.00 to −1.53), p<0.001. (D) Weight z score (mean±95% CI) at maximum period of treatment: intermittent (n=123) weight mean z score 0.79 (95% CI 0.57 to 1.01), daily (n=122) 0.50 (95% CI 0.29 to 0.71), p=0·06. *Maximum period of treatment=single measurement at last follow-up of patients at least 1 year into treatment.

Despite the relative young age of the cohort, in the second decade respiratory and cardiac outcomes showed a decline of LVSF% by 1% and FVC% by 2.2% per annum, irrespective of treatment regimen (see web appendix 3).

A larger proportion of patients on daily GCs reported moderate to severe side effects. Cushingoid features (33% vs 15%), behavioural problems (40% vs 29%) and hypertension (22% vs 9%) were significantly higher in those on daily GC treatment. We highlighted a significantly increased BMI in daily (mean z score 1.99) versus intermittent (mean z score 1.5) treatment, and severe height restriction in daily (mean z score −1.77) compared with intermittent (mean z score −0.70) treatment.

Long-term use of GCs is a recognised and well described risk factor for decreased bone mineral density and increased incidence of vertebral fracture in DMD.[26 30–33] In our studied population, symptomatic vertebral fractures were seen in 8% on daily and 4% on intermittent treatment. A prevalence of up to 32% has previously been reported in smaller series of patients with chronically GC-treated DMD.[34] Asymptomatic vertebral fractures are possibly less likely to be ascertained by the NSCN database. NSCN DEXA scan data (table 3) suggest that applying the standard of care reduces osteopenia, affecting only 8% of boys on daily prednisolone. Nascent and evolving guidelines on bone protection in DMD recommend normalisation of serum 25-hydroxyvitamin-D3 with oral supplements at diagnosis, close surveillance while on GC, annual DEXA scans and intravenous bisphosphonates for symptomatic vertebral fractures.[26] Furthermore, osteopenia/z scores ≤−2.5 require a lateral spine radiograph looking for vertebral deformity, which may require bisphosphonate treatment.[26] The NSCN aims to incorporate these recommendations in the future.

A number of prospective studies have been published on GC treatment in DMD, ranging from cohort studies to randomised double-blind clinical trials (see web appendix 2). Only two studies compared daily with intermittent GC treatment in the short term.[10 22] A recent randomised blinded clinical trial compared high-dose weekend prednisone (10 mg/kg/week) with a standard daily dose (0.75 mg/kg/day) over 12 months in 64 boys with DMD.[10 35] The study provided evidence that high-dose weekend prednisone is equally effective in preserving muscle function for some of the outcome measures, but with increased linear growth and lower BMI.[10 35]

A recent longitudinal multicentre cohort study reported NSAA changes over 12 months in 106 ambulant boys with DMD.[22] A clear slope of change was observed at the age of 7, also confirmed by our findings; above age 7 (n=71); a slower rate of decline was reported in boys on continuous GC. No randomised controlled study has previously reported data on LOA in boys with DMD treated with an intermittent regimen.

Our study has several limitations: incomplete and partially missing data, adjusted for in the statistical analysis; outcome measures and side-effects profile were analysed collectively and not as single patient trajectories; side effects were assessed in the clinic and included parental reports; there was no validated quality of life information; there were no validated measures for learning difficulties and behavioural problems; and analysis did not adjust for severity of phenotype at enrolment. Furthermore, it is difficult to account for the effect of boys treated with GCs whose parents did not give consent for participation, or for incomplete data. Finally, we could not compare outcomes with an untreated cohort, as almost invariably families would agree on starting GCs. Following this study, a more rigorous definition of side effects will be introduced in the NSCN, particularly concerning behavioural problems, using validated psychometric evaluations. Nevertheless, for the first time our analysis provides long-term outcome data from diagnosis to LOA in a large sample representative of the ambulant DMD population in the UK. These data offer evidence for a functional benefit of intermittent prednisolone, possibly more so if initiated early, delaying median LOA to 12 years. This contrasts with the very modest effect of intermittent GCs given to older boys.[4] The intermittent regimen was overall better tolerated with fewer adverse effects.

Although multiple randomised clinical trials remain the gold standard in determining therapeutic safety and efficacy, there is an increasing recognition of the importance of observational studies.[36–39] A robust well designed and properly analysed secure database containing prospectively and systematically acquired data can be a valuable tool for guiding evidence-based decisions in relation to treatment and in designing future controlled trials.[40] Our study provides a framework for consultation when starting treatment. However, it does not offer a definite answer on which GC regimen should be used, and a long-term randomised clinical trial of intermittent versus continuous GC is required. The NSCN will collaborate in an international clinical trial of different steroid regimes funded by the National Institutes of Health (FOR-DMD: Finding the Optimum Regimen of Corticosteroids for DMD), which will compare daily prednisone/deflazacort regimens with intermittent treatment in a young steroid-naïve population in a randomised controlled trial.[41]

A future challenge will be to assess the efficacy and safety profile of continuing GC administration in the non-ambulant population. With the implementation of multidisciplinary interventions, in particular respiratory management, life expectancy has shifted to the third/fourth decades compared with the second/third decades for steroid-naïve patients.[5 6] GCs in DMD are likely to further prolong life. Longitudinal analysis is required to evaluate survival and quality of life in patients with DMD, and to determine the optimal treatment protocol in continuing GC treatment beyond LOA.

In conclusion, our study compared the benefits and tolerability of the most widely used GC regimens in the UK and addresses one of many facets of a multisystem disorder, which is evolving. Further prospective collection of clinical data with a robust and refined tool can significantly facilitate monitoring and improve the standards of care for this common genetic disease.

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Long-term benefits and adverse effects of intermittent versus daily glucocorticoids in boys with Duchenne muscular dystrophy

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