Randomized, blinded trial of weekend vs daily prednisone in Duchenne muscular dystrophy

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Editorial, page 416

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ABSTRACT

Objective: To perform a double-blind, randomized study comparing efficacy and safety of daily and weekend prednisone in boys with Duchenne muscular dystrophy (DMD).

Methods: A total of 64 boys with DMD who were between 4 and 10 years of age were randomized at 1 of 12 centers of the Cooperative International Neuromuscular Research Group. Efficacy and safety of 2 prednisone schedules (daily 0.75 mg/kg/day and weekend 10 mg/kg/wk) were evaluated over 12 months.

Results: Equivalence was met for weekend and daily dosing of prednisone for the primary outcomes of quantitative muscle testing (QMT) arm score and QMT leg score. Secondary strength scores for QMT elbow flexors also showed equivalence between the 2 treatment groups. Overall side effect profiles of height and weight, bone density, cataract formation, blood pressure, and behavior, analyzed at 12 months, did not differ between weekend and daily dosing of prednisone.

Conclusions: Weekend dosing of prednisone is equally beneficial to the standard daily dosing of prednisone. Analysis of side effect profiles demonstrated overall tolerability of both dosing regimens.

Classification of evidence: This study provides Class I evidence that weekend prednisone dosing is as safe and effective as daily prednisone in preserving muscle strength and preventing body mass index increases in boys with DMD over a 12-month period. *Neurology*® 2011;77:444–452

GLOSSARY

ANOVA = analysis of variance; **BMI** = body mass index; **CBCL** = Child Behavior Check List; **CINRG** = Cooperative International Neuromuscular Research Group; **DEXA** = dual-energy x-ray absorptiometry; **DMD** = Duchenne muscular dystrophy; **FEV_1** = forced expiratory volume in 1 second; **FVC** = forced vital capacity; **MIP** = maximum inspiratory pressure; **MMT** = manual muscle testing; **MVV** = maximal voluntary ventilation; **NCI** = National Cancer Institute; **PFT** = pulmonary function test; **QMT** = quantitative muscle testing.

Duchenne muscular dystrophy (DMD) is a progressive muscle disorder due to mutations in the dystrophin gene.[1,2] Current treatments can slow disease progression, prolonging ambulation, and improving quality of life and survival.[3-5] Corticosteroid treatment for DMD[6-12] is recommended by an American Academy of Neurology practice parameter.[13] Furthermore, a recently published standard of care review emphasized the benefit of corticosteroids for DMD.[14,15] In a large DMD natural history study currently run by the Cooperative International Neuromuscular Research Group (CINRG), 85% of participants are steroid-treated.[16,17]

We hypothesized that weekend prednisone dosing would provide equally effective treatment for DMD as standard daily dosing. Furthermore, corticosteroids might be more widely used in DMD if a dosing regimen had fewer side effects, including less weight gain, less effect on linear

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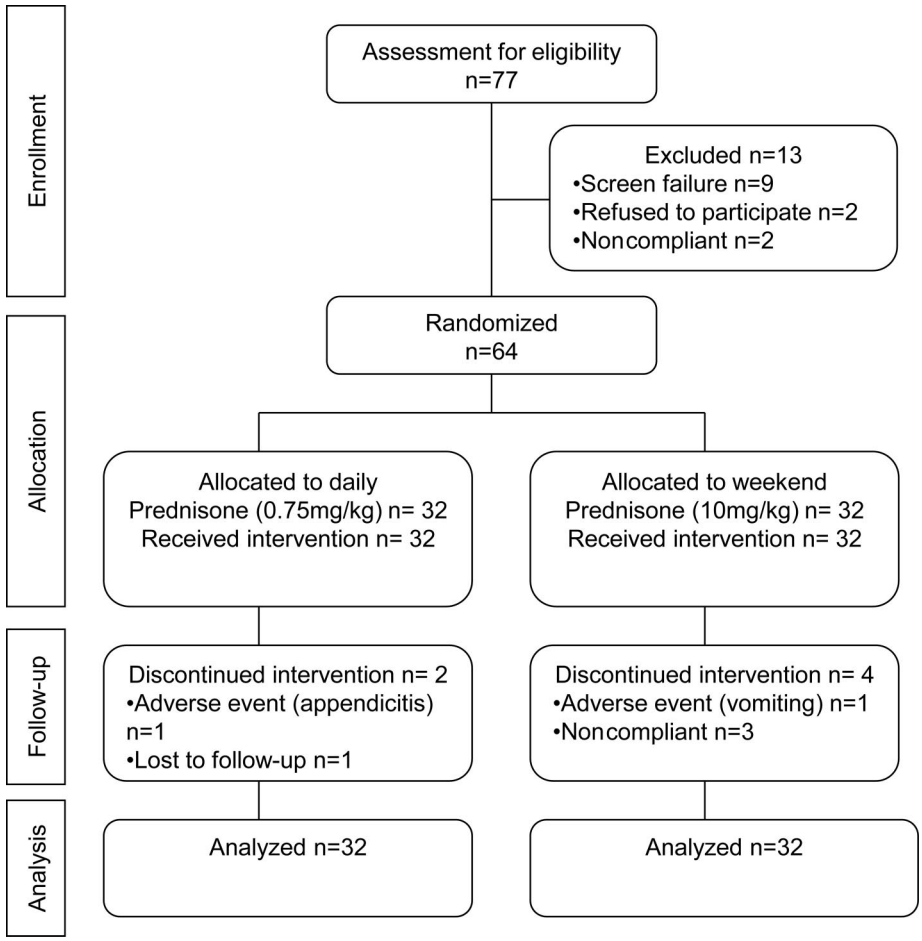
Figure 1 Participant flow through the trial



growth, and fewer behavior problems, while retaining equal effectiveness. In a prior pilot study of 20 boys with DMD, the weekend treatment (10 mg/kg/wk divided over 2 days) produced fewer side effects while retaining the benefits that were observed with daily prednisone.[18] The current randomized, blind study was designed to compare the standard daily dose of prednisone (0.75 mg/kg/d) with the weekend dose that was tested in the pilot study (10 mg/kg/wk divided over 2 days) for boys with DMD age 4 to 10 years.

METHODS

This was a multicenter, international, prospective, 12-month, randomized, double-blind, placebo-controlled, equivalence study enrolled by 12 institutions of the CINRG network.

Standard protocol approvals, registrations, and patient consents. The study was approved by the Institutional Review Board at each institution. Written informed consent and assent were obtained from all participants' parents or caregivers. The trial was registered at the NIH Web site (ClinicalTrials.gov: NCT00110669).

Population. Ambulant, steroid-naive boys with a confirmed diagnosis of DMD, age 4 to 10 years, were included. Other inclusion criteria comprised evidence of muscle weakness by clinical or functional assessment and the ability to provide a reproducible unilateral quantitative muscle testing (QMT) biceps score within 15% of the first assessment.

Exclusion criteria were female DMD carrier status, use of carnitine, other aminoacids, creatine, glutamine, coenzyme Q10, or any herbal supplements within 3 months prior to enrollment, significant concomitant illness including cardiomyopathy, positive response to purified protein derivative, and either no prior exposure to chickenpox or no varicella immunization.

Treatment groups. Participants were randomized into 2 groups: daily dose group, daily prednisone 0.75 mg/kg/d plus placebo on Saturday and Sunday; and weekend dose group, weekend prednisone 5 mg/kg on Saturday and 5 mg/kg on Sunday, plus a daily placebo. Capsules containing prednisone, rounded to the nearest 2.5 mg, or inert filer were obtained from Franck's Pharmacy (Ocala, FL). The CINRG central pharmacy dispensed the study drug. Compliance was monitored at each visit by pill counts and review of medication diaries. Concomitant medications allowed during the study included vitamin D, calcium, ranitidine, and Tums. Participants were advised to follow a high-protein, low-carbohydrate, low-fat diet.

Table 1 Baseline characteristics[a]

Characteristics	Weekend dose		Daily dose		*p* Values
	No. (%)	Mean (SD)	No. (%)	Mean (SD)	
Age, y					
4–6	17	5.8 (0.9)	14	5.7 (0.7)	0.33
7–10	15	8.4 (1.1)	18	8.9 (1.2)	
Race					
Caucasian	17 (53)		17 (53)		1
Asian	6 (19)		6 (19)		
African American	1 (3)		2 (6)		
Other	8 (25)		7 (22)		
Ethnicity					
Hispanic	8 (25)		7 (22)		0.77
Non-Hispanic	24 (75)		25 (78)		
Efficacy					
Muscle strength					
QMT arm score, lb	31	5.9 (2.5)	32	6.9 (3.2)	0.18
QMT leg score, lb	31	9.1 (3.9)	32	10.6 (4.5)	0.13
QMT grip score, lb	31	9.2 (3.2)	32	10.8 (4.8)	0.16
QMT elbow flexors, lb	31	6.5 (2.9)	32	7.6 (3.2)	0.17
QMT elbow extensors, lb	31	5.4 (2.3)	32	6.1 (3.4)	0.22
QMT knee flexors, lb	31	9.3 (3.5)	32	11.3 (4.0)	0.06
QMT knee extensors, lb	31	8.9 (5.8)	32	9.9 (7.1)	0.34
MMT score	29	222 (35)	29	232 (36)	0.17
Timed tests					
10-m walk (log seconds)	31	2.1 (0.4)	31	1.9 (0.4)	0.21
4-step climb (log seconds)	30	1.9 (0.7)	31	1.8 (0.8)	0.51
Supine to standing (log seconds)	25	2.0 (0.5)	26	2.1 (0.8)	0.74
Pulmonary function					
FVC % predicted	18	84 (20)	19	88 (22)	0.86
FEV_1 % predicted	18	86 (20)	19	99 (23)	0.10
MVV	15	27.5 (10.6)	16	32.2 (12.0)	0.36
MIP	25	40.3 (13.2)	21	39.8 (17.9)	0.56
Mobility function scales					
Brooke, upper extremity	32	1.3 (0.6)	32	1.2 (0.6)	0.31
Vignos, lower extremity	32	1.9 (1.2)	32	1.7 (1.1)	0.39
Safety					
Anthropometrics					
BMI, kg/m^2	31	16.1 (1.9)	32	16.6 (2.8)	0.40
Height, cm	31	117 (11)	32	120 (12)	0.5
Weight, kg	32	22.4 (5.3)	32	24.4 (8.4)	0.40
Vital signs					
Systolic blood pressure, mm Hg	30	104 (12)	31	106 (16)	0.80
Diastolic blood pressure, mm Hg	30	60 (7)	31	64 (9)	0.15
Blood glucose, mg/dL	32	79.5 (14.2)	31	83.7 (9.4)	0.18
DEXA					
Lumbar spine Z score	26	−1.15 (0.72)	26	−1.12 (0.85)	0.95

—Continued

Criteria for dose reduction. Prednisone/placebo dose was reduced for 1) an increase in body mass index (BMI) (kg/m^2) greater than 10% over 3 months; 2) a fasting blood sugar greater than 100 mg/dL after dietary modification; 3) an increase in diastolic blood pressure greater than 10 mm Hg over upper limit of normal for age; 4) an increase in systolic blood pressure greater than15 mm Hg since last visit, after 1 month of low sodium diet; and 5) otherwise nonmanageable side-effects.

Endpoints. The study's 2 primary efficacy endpoints were upper and lower extremity muscle strength as measured by the QMT scores (the summation of maximal isometric voluntary contraction force of both flexors and extensors of elbow and knee). All evaluators performing testing were certified for inter-rater reliability by standard CINRG protocol.[19,20] Secondary efficacy endpoints included individual QMT scores, grip strength, manual muscle testing (MMT) score (modified Medical Research Council scale), timed function tests (time to run/walk 10 meters, time to climb 4 standard steps, and time to get up from supine position on the floor), the modified Brooke and Vignos scales, and pulmonary function tests (PFTs) that comprised percent predicted forced vital capacity (FVC % predicted), percent predicted forced expiratory volume in 1 second (FEV_1 % predicted), maximal voluntary ventilation (MVV), and maximum inspiratory pressure (MIP).[21,22] PFTs were performed only by participants who were at least 6 years old at baseline.

The primary safety endpoint was change in BMI. Secondary safety endpoints included weight, height, blood pressure, cataracts, lumbar spine Z score, measured by dual-energy x-ray absorptiometry (DEXA), and behavior, assessed by the Child Behavior Check List (CBCL).[23] Syndrome subscales in the CBCL are T scores standardized such that values over 70 are clinically significant.

A total of 8 visits took place at the following timepoints: 2 screening visits, month 1, 3, 6, 9, 12, and post study visit (within 1 week of the month 12 visit). At each visit, participants completed assessments, safety laboratory panels, physical and neurologic examination, and adverse event review. The DEXA and ophthalmology assessments were only completed at baseline and month 12 visits. Recruitment took place over 3 years beginning November 2003; the last participant completed the study in November 2007.

Randomization. Eligible participants were randomized by the CINRG Coordinating Center within site and equal-sized age stratum (4–6 years, 7–10 years) using a random permuted block randomization scheme (block sizes 2 and 4).

Statistical analysis. Averages of results from the 2 screening visits and the 2 12-month visits were used to assess primary outcome. Baseline characteristics for efficacy and safety outcomes were summarized using means and standard deviations and compared between the 2 groups using 2-way analysis of variance (ANOVA) with treatment as one factor and age stratum as the second factor.

In order to test the primary hypothesis of efficacy equivalence, an observed cases analysis was employed. The equivalence limit was defined using the baseline data and choosing an equivalence limit of approximately 1 SD or less of the baseline distribution for muscle strength tests and percent predicted PFTs. For MMT score the equivalence limit was defined as one point on the 10-point scale for each of 34 muscles tested. This resulted in an equivalence width of ±2 pounds for the muscle strength tests, ±17 points of the MMT score, and ±10% on the percent predicted PFTs. For each endpoint, the observed difference from

Table 1 Continued

Characteristics	Weekend dose		Daily dose		*p* Values
	No. (%)	Mean (SD)	No. (%)	Mean (SD)	
Child Behavioral Check List (T scores)					
Total problems	28	52 (7)	27	55 (11)	0.19
Internalizing	28	55 (10)	27	56 (10)	0.68
Externalizing	28	50 (10)	27	55 (10)	0.03
Anxious/depressed	28	52 (11)	27	55 (14)	0.48
Somatic complaints	28	53 (9)	27	54 (14)	0.70
Withdrawn/depressed	28	55 (12)	27	56 (13)	0.93
Attention problems	28	51 (9)	27	56 (13)	0.10
Aggressive behavior	28	48 (9)	27	54 (9)	0.01

Abbreviations: BMI = body mass index; DEXA = dual-energy x-ray absorptiometry; FEV_1 = forced expiratory volume in 1 minute; FVC = forced vital capacity; MIP = maximum inspiratory pressure; MMT = manual muscle testing; MVV = maximal voluntary ventilation; QMT = quantitative muscle testing.

[a] Values are averages of 2 screening visits that were performed within 7 days from each other. *p* Values for continuous outcomes are based on the main treatment effect in a 2-way analysis of variance. *p* Values for the categorical outcomes (race and ethnicity) are based on exact χ^2 tests.

baseline (+SD) and the 95% confidence limits of the differences in changes between treatments were calculated. If the difference in the magnitude of the changes from baseline between the 2 treatment groups was small (close to zero), this implied the treatments were equivalent. Two one-sided *t* tests were done to test whether the difference of changes was higher than the lower bound of equivalence and lower than the higher bound of equivalence simultaneously. If both *p* values were less than or equal to 0.025, this implied that equivalence was established between treatments. Timed function tests had skewed distributions; therefore, in order to analyze the equivalence of change from baseline to 12 months for timed function tests, a log transformation of the data was performed, and the boundaries of equivalence defined as ±0.4 log seconds. If a participant could not perform the timed test at 12 months due to disease progression, we imputed a value of 30 seconds for the 10-meter walk, 45 seconds for the 4-step climb, and 45 seconds for supine to stand.

An additional analysis was performed on the group of participants who both completed the study and in whom there were no dose reductions.

The hypothesis that the weekend dosing regimen would cause fewer side effects than the daily dosing regimen was tested using 2-way ANOVA. The main treatment effect was assessed comparing type of treatment (weekend vs daily) and, secondarily, treatment by age group interaction. In addition, exploratory analyses examine repeated BMI measurements over time for each participant using linear mixed effects models.[24] Frequency, body system, severity, and relationship to drug of adverse events were assessed using the National Cancer Institute's (NCI) Common Toxicity Criteria.[25]

Statistical analyses were performed by using SAS institute SAS/STAT software 9.1[26] and EquivTest PK v.3.[27]

RESULTS

Baseline. Twelve institutions screened 77 participants of whom 64 were eligible and randomized (figure 1). Baseline characteristics are provided in table 1. The mean age of all screened participants was 7.1 years and the median age was 6.9 years. The mean age of all randomized participants was 7.3 years and the median age was 7.2 years. Thirty-four (53%) of the participants were Caucasian, 3 (5%) were African American, 12 (19%) were Asian, and 15 (23%) were from other races. CBCL T scores of aggressive behavior and externalizing were the only significant differences at baseline and were not believed to be clinically meaningful; thus, the randomization procedure was successful.

Efficacy. For the primary efficacy outcomes for muscle strength of QMT arm score and QMT leg score, equivalence between the 2 groups was met with both groups showing improved strength (table 2). Secondary muscle strength outcomes for QMT elbow flexors also showed equivalence, and QMT elbow extensors showed borderline equivalence. Equivalence was not met for secondary muscle strength outcomes MMT, QMT grip, and QMT knee tests. Timed tests for 10-meter walk, 4-step climb, and supine to stand were equivalent between the 2 groups.

Two other secondary efficacy outcomes, FVC and FEV_1, did not show equivalence between the 2 groups (table 2).

Safety. The side effect profiles of the 2 groups were virtually identical at 12 months with no significant differences in the assessments of anthropometrics, vital signs, DEXA, and CBCL (table 3). Importantly, there was no significant difference in the primary safety endpoint, BMI, comparing daily with weekend dosing at 12 months.

There were 6 prednisone dose reductions in 5 participants in the study. In the daily group, 3 participants had dose reductions because of BMI increase and one participant because of behavior problems. In the weekend group, one participant had 2 dose reductions, one for BMI increase and one for cushingoid features.

BMI changes were also analyzed within each age stratum over time and using the piecewise linear mixed effects model, allowing for a change in slope of BMI at 3 months of treatment within treatment and age groups (figure 2). Although these analyses did not achieve statistical significance, for participants 4–6 years old, we observed a numeric difference toward a larger increase in BMI on the daily dose compared to the weekend dose during the first 3 months of treatment. In the 7- to 10-year-old participants, there was a visual numeric difference, which while not significant, suggested a greater increase in BMI on the daily dose.

Although there was no significant difference between the 2 groups for height measured at 12 months (table 3), there was a significant increase in linear growth over 12 months in the weekend group com-

Table 2 Changes in efficacy from baseline to 12 months on treatment and equivalence evaluations

Characteristics	Change from baseline to month12				Defined equivalence limits from 0	Difference between means (95% confidence interval)	*p* Values[a]	
	Weekend dose		Daily dose					
	No. (%)	Mean (SD)	No. (%)	Mean (SD)			Lower	Upper
Muscle strength								
QMT arm score, lb	27	0.7 (1.7)	30	1.3 (2.4)	±2	−0.6 (−1.7, 0.6)	0.009	<0.0001
QMT leg score, lb	27	2.2 (3.7)	30	2.1 (3.4)	±2	0.09 (−1.8, 2.0)	0.01	0.02
QMT elbow flexors, lb	27	0.9 (1.9)	30	1.3 (2.7)	±2	−0.3 (−1.6, 0.9)	0.005	0.0002
QMT elbow extensors, lb	27	0.5 (1.7)	30	1.4 (2.5)	±2	−0.9 (−2.0, 0.3)	0.027	<0.0001
QMT knee flexors, lb	27	2.5 (3.5)	30	1.1 (3.8)	±2	1.4 (−0.6, 3.3)	0.0005	0.26
QMT knee extensors, lb	27	1.8 (4.6)	30	3.0 (4.3)	±2	−1.2 (−3.6, 1.2)	0.25	0.005
QMT grip score, lb	27	2.5 (2.4)	30	4.2 (3.4)	±2	−1.6 (−3.2, −0.1)	0.32	<0.0001
MMT score	27	4 (24.3)	27	−0.6 (23.2)	±17	4.4 (−8.5, 17.4)	0.0008	0.03
Timed tests								
10 m walk (log seconds)	27	0.1 (0.4)	29	0.1 (0.4)	±0.4	0.004 (−0.2, 0.2)	0.0004	0.0005
4 step climb (log seconds)	26	−0.06 (0.3)	29	−0.06 (0.5)	±0.4	−0.0002 (−0.2, 0.2)	0.0009	0.0008
Supine to standing (log seconds)	21	−0.05 (0.3)	25	−0.2 (0.3)	±0.4	0.18 (0.003, 0.4)	<0.0001	0.01
Pulmonary function								
FVC % predicted	15	5 (15.7)	16	0.6 (24.0)	±10	4.6 (−9.8, 19.1)	0.03	0.23
FEV_1 % predicted	15	2 (22.5)	16	−4 (20.4)	±10	6.1 (−9.1, 20.4)	0.02	0.31
MVV	12	2 (6)	15	−2 (9)	±10	3.6 (−2.5, 9.8)	0.0001	0.02
MIP	23	9 (12)	19	9 (13)	±10	0.3 (−7.4, 8.0)	0.005	0.008
Mobility function scale								
Brooke, upper extremity	28	−0.1 (0.4)	30	0.2 (0.5)	±0.3	−0.3 (−0.5, −0.03)	0.41	<0.0001
Vignos, lower extremity	28	0.6 (1.4)	30	0.5 (1.4)	±0.6	0.04 (−0.7, 0.8)	0.04	0.06

Abbreviations: FEV_1 = forced expiratory volume in 1 minute; FVC = forced vital capacity; MIP = maximum inspiratory pressure; MMT = manual muscle testing; MVV = maximal voluntary ventilation; QMT = quantitative muscle testing.

[a] *p* Values are calculated for 2 one-sided tests on upper and lower boundaries of equivalence. For example, for QMT arm score, the first null hypothesis is that the change in the score for weekend dose group minus the change in the daily dose group is −2 lb or a more negative number, and this hypothesis is rejected in favor of the alternative hypothesis that this difference in changes is less negative than −2 lb ($p = 0.009$). The second null hypothesis is that the change in the weekend dose group minus the change in the daily dose group is larger than 2 lb, and is rejected in favor of the alternative hypothesis that the change is smaller than 2 lb ($p < 0.0001$). In addition, the table provides the estimated 95% confidence intervals of the difference in changes from baseline or between the 2 treatments.

pared to the daily group (mean change in daily dose group of 4.1 cm and in the weekend dose group of 6.6 cm, $p = 0.002$).

There was no significant difference in the lumbar Z score between the weekend and daily groups at 12 months of treatment (table 3). However, there was a significant difference for change in lumbar Z score from baseline to 12 months favoring the weekend dosing (Z score change of −0.30 in the daily dose and of +0.26 in the weekend dose group, $p = 0.001$).

Adverse events were assessed using the NCI Common Toxicity Criteria[25] and analyzed descriptively recognizing limitations of sample size. There were 6 events in each group assigned grade 3 or 4. Five of 6 events in the weekend group and 4 of 6 events in the daily group were progression of weakness and considered not related to study drug. There was one severe case of flu and fever in the weekend group. There was one participant with acute appendicitis and one participant with a scalp laceration in the daily group. Overall, there were no significant differences in number or grade of adverse events between the 2 groups.

Study discontinuations. One participant in each group discontinued from the study prior to or at the first return visit (month 1) because of an adverse event. In the daily group, the participant with appendicitis discontinued and in the weekend group, one participant discontinued due to severe vomiting. Overall, 6 participants withdrew before the end of the study (4 in the weekend group and 2 in the daily group). An additional analysis excluded the 5 participants with dose reductions. Results remained substantially the same (data not shown).

Table 3 Side effect profiles at 12 months

Characteristics	Weekend dose		Daily dose		
	No.	Mean (SD)	No.	Mean (SD)	*p* Values[a]
Anthropometrics					
BMI, kg/m^2	28	17.8 (3.3)	30	19.6 (4.2)	0.12
Height, cm	28	124 (11)	30	123 (11)	0.27
Weight, kg	28	28.2 (8.5)	30	30.7 (11.4)	0.53
Vitals					
Systolic blood pressure, mm Hg	28	110 (11)	30	112 (16)	0.75
Diastolic blood pressure, mm Hg	28	61 (8)	30	64 (9)	0.20
Blood glucose, mg/dL	25	84.9 (10.2)	26	88.0 (13.6)	0.44
DEXA					
Lumbar spine Z scores	25	−0.88 (0.85)	28	−1.33 (0.91)	0.06
Child Behavioral Check List					
Total problems	26	49 (10)	28	48 (10)	0.53
Internalizing	26	52 (9)	28	48 (9)	0.11
Externalizing	26	50 (11)	28	51 (10)	0.83
Anxious/depressed	26	47 (8)	29	48 (7)	0.78
Somatic complaints	26	50 (7)	29	48 (9)	0.24
Withdrawn/depressed	26	50 (9)	29	46 (7)	0.05
Attention problems	26	48 (10)	30	46 (6)	0.48
Aggressive behavior	26	48 (9)	29	47 (8)	0.81

Abbreviations: BMI = body mass index; DEXA = dual-energy x-ray absorptiometry.
[a] *p* Values by 2-way analysis of variance.

DISCUSSION Following the original demonstration of efficacy of prednisone for DMD by the Clinical Investigation of Duchenne Dystrophy group,[28] several randomized, controlled trials refined daily dosing of prednisone for DMD.[8,12] A further study did not support efficacy of alternate day dosing.[29] A pilot study and a randomized, controlled, crossover trial (sample size 17) demonstrated efficacy of prednisone dosing limited to the first 10 days of the month.[30,31] A pilot study of weekend prednisone dosing demonstrating beneficial effects on strength preservation, but fewer side effects than daily prednisone, provided the rationale for the current randomized, controlled study.[18]

The current study demonstrated that weekend dosing of prednisone for DMD was equivalent to daily dosing over 12 months based on the study-defined, primary efficacy outcome of quantitative leg and arm muscle strength and no significant difference in the primary safety outcome of BMI. This randomized, controlled study adds to the body of evidence supporting the use of corticosteroid treatment for DMD and expands the clinical dosing options for prednisone treatment of DMD.[12]

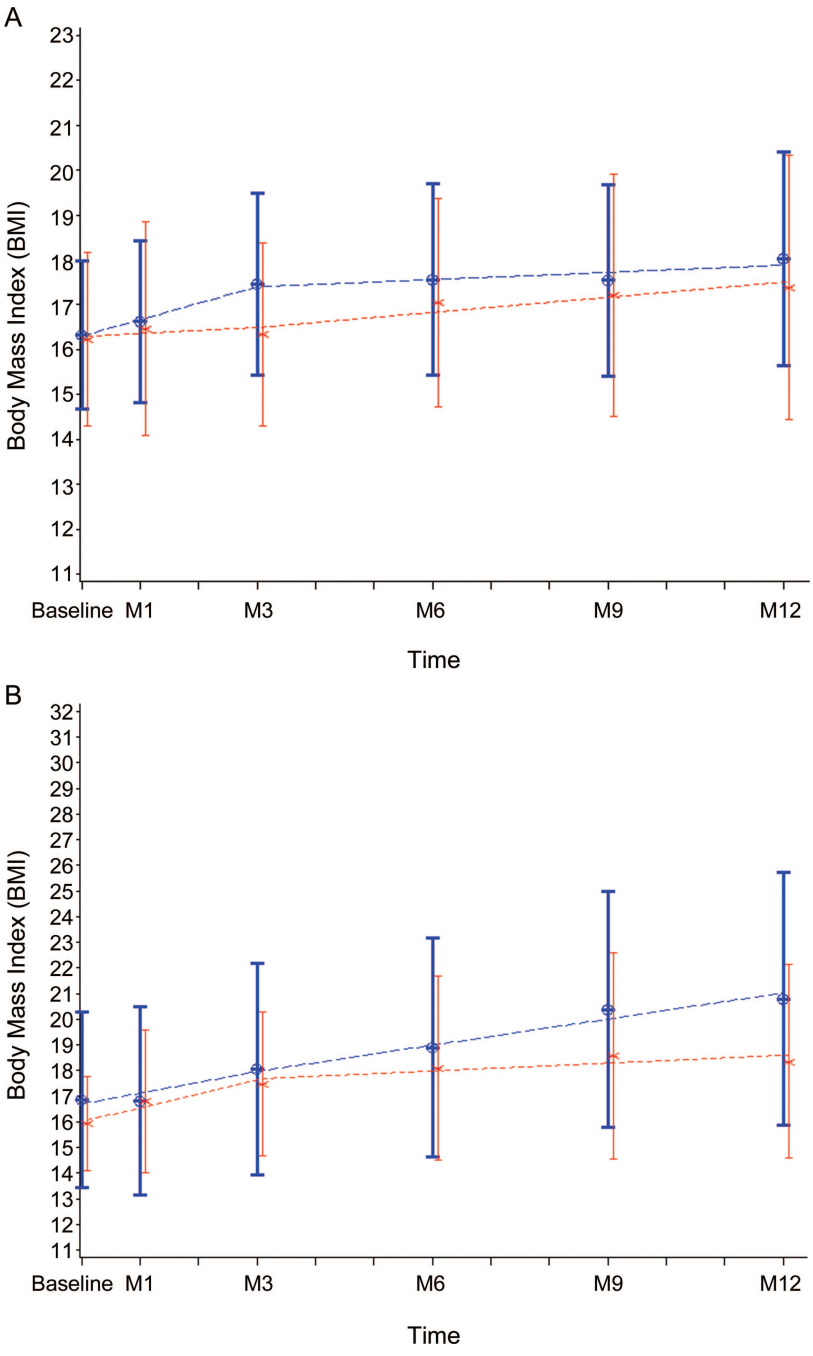
The current study also examined secondary efficacy outcomes comprising strength assessments by MMT and QMT of several individual muscle groups and demonstrated equivalence of QMT elbow flexor scores between the 2 groups. QMT elbow extensor, MMT, QMT grip score, and QMT knee scores did not meet equivalence. PFT results demonstrated variability and achieved equivalence for MVV and MIP, but not for FVC % predicted and FEV_1 % predicted.

The most common adverse effect of corticosteroid use in patients with DMD is weight gain, which increases the mechanical load on weakening muscles and likely contributes to cessation of ambulation.[32] BMI was above the 50th percentile for the mean age of our population at baseline.[33] This finding alone suggests that caloric intake monitoring is important for patients with DMD. In this study we showed that the primary safety outcome measure, BMI, was not significantly different between the daily and weekend dosing groups at 12 months. Although the study was not powered to establish patterns of BMI change, different effects on BMI emerged from age group subanalysis. Numeric, but not statistically significant, differences observed in figure 2 suggested that older participants with DMD (7–10 years) had a greater increase in BMI than younger participants (4–6 years) with both dose regimens, although more so with the daily dose regimen, possibly due in part to decreased physical activity. Furthermore, the temporal pattern of weight gain in the younger participants (4–6 years) appeared different between the daily and weekend dosing groups, with earlier and greater weight gain with the daily dosing group.

Weekend prednisone dosing was associated with significantly greater linear growth than daily dosing. Although patients with DMD have a normal length and weight at birth,[34] delayed growth starts during the first years of life and median height of patients with DMD is slightly less than the 50th percentile before age 10 years. By age 18 years, median height is less than the 5th percentile.[35]

Osteopenia is common in children with neuromuscular disorders, who have an increased incidence of pathologic fractures.[32,36] During 12 months of treatment, weekend and daily prednisone dosing were each associated with small changes in lumbar spine Z score, thus alleviating a common concern that corticosteroid treatment in patients with DMD increases the risk of osteoporosis. Increases in muscle strength and activity induced by prednisone treatment may stabilize bone density, as supported by the current study and postulated previously.[32,37-40] However, a longer study would be required to adequately assess the effects of corticosteroid use on bone metabolism and fracture risk. Furthermore, we did not assess femoral bone density, which has been shown to be abnormal even in younger ambulant boys with

Figure 2 **Linear mixed effects models for body mass index (BMI) measurements over time**



BMI trends by age group for age 4–6 years (A) and 7–10 years (B) are plotted over time. Results on daily dosing are in blue and weekend dosing are in red. Means and standard deviations at each study visit and fitted means are shown.

DMD and to correlate with increased risk of lower extremity fractures.[39]

Corticosteroid-induced behavior changes, including hyperactivity, depression, or psychosis, are commonly accepted symptoms in patients with DMD that may limit treatment.[15] In our study we found no clinically significant baseline behavioral abnormalities. Both daily and weekend prednisone dosing resulted in similar CBCL scores after 12 months of treatment with neither group showing worsening of behavior on therapy. No participants discontinued the study because of behavioral adverse effects although one participant on daily dosing had a dose reduction due to behavioral problems.

A limitation of this study was the 12-month duration of treatment. However, most study participants transitioned into a large multicenter observational study of DMD that will provide long-term follow-up to further inform treatment decisions.

Overall, this randomized, blind placebo-controlled study demonstrated equivalent efficacy of weekend prednisone dosing for DMD as standard daily dosing. Although there was no significant difference in the primary safety outcome of BMI between the groups, there appeared to be significant increases in linear growth and bone mineral density favored by the weekend dose regimen. Most importantly, the finding of equivalently effective but different dosing regimens with similar safety profiles provides clinicians treating patients with DMD with alternative therapeutic options that may aid some families to adjust to corticosteroid treatment, which is of proven benefit for prolonging ambulation in DMD.

AUTHOR CONTRIBUTIONS

Dr. Escolar: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding. L.P. Hache: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision, study monitoring and grant reports. Dr. Clemens: drafting/revising the manuscript, analysis or interpretation of data. Dr. Cnaan: drafting/revising the manuscript, analysis or interpretation of data, statistical analysis. Dr. McDonald: drafting/revising the manuscript, analysis or interpretation of data, contribution of vital reagents/tools/patients, acquisition of data, study supervision. Dr. Viswanathan: analysis or interpretation of data, acquisition of data, study supervision. Dr. Kornberg: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, study supervision. Dr. Bertorini: drafting/revising the manuscript, acquisition of data. Dr. Nevo: drafting/revising the manuscript, study concept or design, acquisition of data. Dr. Lotze: drafting/revising the manuscript, acquisition of data, study supervision. Dr. Pestronk: drafting/revising the manuscript, study concept or design, study supervision. Dr. Ryan: study concept or design, analysis or interpretation of data, acquisition of data, study supervision. Dr. Monasterio: study concept or design, acquisition of data. Dr. Day: study concept or design, contribution of vital reagents/tools/patients, acquisition of data. A. Zimmerman: drafting/revising the manuscript, study concept or design, acquisition of data, study supervision. A. Arrieta: drafting/revising the manuscript, analysis or interpretation of data, acquisition of data, statistical analysis, study supervision. E. Henricson: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision, obtaining funding. J. Mayhew: study concept or design, acquisition of data, study supervision. Dr. Florence: study concept or design, acquisition of data, study supervision. F. Hu: analysis or interpretation of data, statistical analysis. Dr. Connolly: drafting/revising the manuscript, study concept or design, analysis or interpretation of data, acquisition of data, study supervision.

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DISCLOSURE

Dr. Escolar serves on a scientific advisory board for the NIH/NINDS; serves on the speakers' bureau for and has received funding for travel and speaker honoraria from Athena Diagnostics, Inc.; serves as a consultant for Acceleron Pharma, HALO therapeutics, AVI Biopharma, Gerson Lheman Group (GLC), and Medacorp; and has received research support from the NIH, the Muscular Dystrophy Association, and the Foundation to Eradicate Duchenne (FED). L.P. Hache serves on the CINRG Executive Committee, CINRG Publication and Outcomes Subcommittees, and Treat-NMD Global Database Oversight Committee; and has received research/salary support from Genzyme Corporation, the US Department of Defense, and the NIH. Dr. Clemens receives/has received research support from Genzyme Corporation, Amicus Therapeutics, Inc., the US Department of Defense, the US Department of Veterans Affairs, and the NIH. 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REFERENCES

1. Emery AE. Population frequencies of inherited neuromuscular diseases: a world survey. Neuromuscul Disord 1991;1:19–29.
2. Tuffery S, Chambert S, Bareil C, et al. Mutation analysis of the dystrophin gene in Southern French DMD or BMD families: from Southern blot to protein truncation test. Hum Genet 1998;102:334–342.
3. Escolar DM, Buyse G, Henricson E, et al. CINRG randomized controlled trial of creatine and glutamine in Duchenne muscular dystrophy. Ann Neurol 2005;58:151–155.
4. Fenichel G, Pestronk A, Florence J, Robison V, Hemelt V. A beneficial effect of oxandrolone in the treatment of Duchenne muscular dystrophy: a pilot study. Neurology 1997;48:1225–1226.
5. Tarnopolsky MA, Mahoney DJ, Vajsar J, et al. Creatine monohydrate enhances strength and body composition in Duchenne muscular dystrophy. Neurology 2004;62:1771–1777.
6. 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.
7. Biggar WD, Harris VA, Eliasoph L, Alman B. Long-term benefits of deflazacort treatment for boys with Duchenne muscular dystrophy in their second decade. Neuromuscul Disord 2006;16:249–255.

8. Griggs RC, Moxley RT III, Mendell JR, et al. Prednisone in Duchenne dystrophy: a randomized, controlled trial defining the time course and dose response: Clinical Investigation of Duchenne Dystrophy Group. Arch Neurol 1991;48:383–388.
9. Griggs RC, Moxley RT III, Mendell JR, et al. Duchenne dystrophy: randomized, controlled trial of prednisone (18 months) and azathioprine (12 months). Neurology 1993; 43:520–527.
10. Manzur AY, Kuntzer T, Pike M, Swan A. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Cochrane Database Syst Rev 2008;CD003725.
11. Markham LW, Kinnett K, Wong BL, Woodrow BD, Cripe LH. Corticosteroid treatment retards development of ventricular dysfunction in Duchenne muscular dystrophy. Neuromuscul Disord 2008;18:365–370.
12. 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.
13. Moxley RT, III, Ashwal S, Pandya S, et al. Practice parameter: corticosteroid treatment of Duchenne dystrophy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology 2005;64:13–20.
14. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 2: implementation of multidisciplinary care. Lancet Neurol 2010;9:177–189.
15. Bushby K, Finkel R, Birnkrant DJ, et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol 2010;9:77–93.
16. Henricson E, McDonald C, Abresch RT, et al. A Cooperative International Neuromuscular Research Group (CINRG) study of the relationship between impairment, activity limitation, participation and quality of life in persons with confirmed dystrophinopathies: one year follow-up of skeletal muscle strength and timed motor performance. Neurology 2010;74:A110. Abstract.
17. McDonald C, Henricson E, Abresch RT, et al. Functional motor performance characteristics of boys with duchenne muscular dystrophy by age groups and steroid use: one-year data from the CINRG longitudinal study project. Neurology 2010;74:A219. Abstract.
18. Connolly AM, Schierbecker J, Renna R, Florence J. High dose weekly oral prednisone improves strength in boys with Duchenne muscular dystrophy. Neuromuscul Disord 2002;12:917–925.
19. Escolar DM, Henricson EK, Mayhew J, et al. Clinical evaluator reliability for quantitative and manual muscle testing measures of strength in children. Muscle Nerve 2001;24:787–793.
20. Mayhew JE, Florence JM, Mayhew TP, et al. Reliable surrogate outcome measures in multicenter clinical trials of Duchenne muscular dystrophy. Muscle Nerve 2007;35:36–42.
21. Vignos PJ Jr, Spencer GE Jr, Archibald KC. Management of progressive muscular dystrophy in childhood. JAMA 1963;184:89–96.
22. Brooke MH, Griggs RC, Mendell JR, Fenichel GM, Shumate JB, Pellegrino RJ. Clinical trial in Duchenne dystrophy: I: the design of the protocol. Muscle Nerve 1981; 4:186–197.
23. Achenbach TM, Rescorla LA. Manual for ASEBA School-Age Forms and Profiles. Burlington, VT: University of Vermont, Research Center for Children, Youth and Families; 2001.
24. Fitzmaurice G, Davidian M, Verbeke G, Molenberghs G. Longitudinal Data Analysis. Boca Raton, FL: Chapman & Hall/CRC Press; 2009.
25. Cancer Therapy Evaluation Program, Common Terminology Criteria for Adverse Events, Version 3.0, DCTD, NCI, NIH, DHHS. March 31, 2003. Available at: http://ctep.cancer.gov. Publication date: August 9, 2006.
26. SAS. Cary, NC: SAS Institute Inc.; 2009.
27. EquivTest/PK test. Saugus, MA: Statistical Solutions Ltd.; 2009.
28. Brooke MH, Fenichel GM, Griggs RC, et al. Clinical investigation of Duchenne muscular dystrophy: interesting results in a trial of prednisone. Arch Neurol 1987;44:812–817.
29. Fenichel GM, Mendell JR, Moxley RT III, et al. A comparison of daily and alternate-day prednisone therapy in the treatment of Duchenne muscular dystrophy. Arch Neurol 1991;48:575–579.
30. Beenakker EA, Fock JM, Van Tol MJ, et al. Intermittent prednisone therapy in Duchenne muscular dystrophy: a randomized controlled trial. Arch Neurol 2005;62:128–132.
31. Sansome A, Royston P, Dubowitz V. Steroids in Duchenne muscular dystrophy: pilot study of a new low-dosage schedule. Neuromuscul Disord 1993;3:567–569.
32. Bianchi ML, Mazzanti A, Galbiati E, et al. Bone mineral density and bone metabolism in Duchenne muscular dystrophy. Osteoporos Int 2003;14:761–767.
33. Mei Z, Grummer-Strawn LM, Pietrobelli A, Goulding A, Goran MI, Dietz WH. Validity of body mass index compared with other body-composition screening indexes for the assessment of body fatness in children and adolescents. Am J Clin Nutr 2002;75:978–985.
34. Rapaport D, Colletto GM, Vainzof M, Duaik MC, Zatz M. Short stature in Duchenne muscular dystrophy. Growth Regul 1991;1:11–15.
35. McDonald CM, Abresch RT, Carter GT, et al. Profiles of neuromuscular diseases: Duchenne muscular dystrophy. Am J Phys Med Rehabil 1995;74:S70–S92.
36. Bachrach LK. Taking steps towards reducing osteoporosis in Duchenne muscular dystrophy. Neuromuscul Disord 2005;15:86–87.
37. Aparicio LF, Jurkovic M, DeLullo J. Decreased bone density in ambulatory patients with Duchenne muscular dystrophy. J Pediatr Orthop 2002;22:179–181.
38. Douvillez B, Braillon P, Hodgkinson I, Berard C. Pain, osteopenia and body composition of 22 patients with Duchenne muscular dystrophy: a descriptive study. Ann Readapt Med Phys 2005;48:616–622.
39. Larson CM, Henderson RC. Bone mineral density and fractures in boys with Duchenne muscular dystrophy. J Pediatr Orthop 2000;20:71–74.
40. Palmieri GM, Bertorini TE, Griffin JW, Igarashi M, Karas JG. Assessment of whole body composition with dual energy x-ray absorptiometry in Duchenne muscular dystrophy: correlation of lean body mass with muscle function. Muscle Nerve 1996;19:777–779.