Title

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Journal

Neurology, 85(12)

ISSN

0028-3878

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Publication Date

2015-09-22

DOI

10.1212/wnl.0000000000001950

Peer reviewed

Prednisone/prednisolone and deflazacort regimens in the CINRG Duchenne Natural History Study

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ABSTRACT

Objective: We aimed to perform an observational study of age at loss of independent ambulation (LoA) and side-effect profiles associated with different glucocorticoid corticosteroid (GC) regimens in Duchenne muscular dystrophy (DMD).

Methods: We studied 340 participants in the Cooperative International Neuromuscular Research Group Duchenne Natural History Study (CINRG-DNHS). LoA was defined as continuous wheelchair use. Effects of prednisone or prednisolone (PRED)/deflazacort (DFZ), administration frequency, and dose were analyzed by time-varying Cox regression. Side-effect frequencies were compared using χ^2 test.

Results: Participants treated ≥1 year while ambulatory (n = 252/340) showed a 3-year median delay in LoA ($p < 0.001$). Fourteen different regimens were observed. Nondaily treatment was common for PRED (37%) and rare for DFZ (3%). DFZ was associated with later LoA than PRED (hazard ratio 0.294 ± 0.053 vs 0.490 ± 0.08, $p = 0.003$; 2-year difference in median LoA with daily administration, $p < 0.001$). Average dose was lower for daily PRED (0.56 mg/kg/d, 75% of recommended) than daily DFZ (0.75 mg/kg/d, 83% of recommended, $p < 0.001$). DFZ showed higher frequencies of growth delay ($p < 0.001$), cushingoid appearance ($p = 0.002$), and cataracts ($p < 0.001$), but not weight gain.

Conclusions: Use of DFZ was associated with later LoA and increased frequency of side effects. Differences in standards of care and dosing complicate interpretation of this finding, but stratification by PRED/DFZ might be considered in clinical trials. This study emphasizes the necessity of a randomized, blinded trial of GC regimens in DMD.

Classification of evidence: This study provides Class IV evidence that GCs are effective in delaying LoA in patients with DMD. *Neurology*® 2015;85:1048–1055

GLOSSARY

CINRG = Cooperative International Neuromuscular Research Group; **DFZ** = deflazacort; **DMD** = Duchenne muscular dystrophy; **DNHS** = Duchenne Natural History Study; **GC** = glucocorticoid corticosteroid; **HR** = hazard ratio; **LoA** = loss of ambulation; **PRED** = prednisone or prednisolone.

Duchenne muscular dystrophy (DMD) is caused by *DMD* gene mutations leading to the absence of dystrophin in skeletal muscle.[1] While dystrophin-restoring treatments are being developed, the only recommended[2,3] pharmacologic intervention is glucocorticoid corticosteroid (GC) treatment,[4–11] with prednisone or its active metabolite prednisolone (PRED), or deflazacort (DFZ). Mechanisms of action include anti-inflammation/immunosuppression,[12] membrane stabilization,[13] enhanced regeneration,[14–16] and gene expression modulation.[17] Side effects are common but usually manageable.[18]

Long-term efficacy of GCs in delaying loss of independent ambulation (LoA) and other "disease milestones," although well described,[9,19–21] is supported more by lower-class evidence than short-term effects on muscle strength and timed function tests. Baseline data from the Cooperative International Neuromuscular Research Group Duchenne Natural History Study

Supplemental data at Neurology.org

From the Children's National Medical Center (L.B., H.G.-D., L.P.M., T.D., E.P.H., A.C.), Washington, DC; University of California Davis Medical Center (E.K.H., C.M.M.), Sacramento, CA; and The George Washington University (E.P.H., A.C.), Washington, DC.

CINRG coinvestigators are listed on the *Neurology*® Web site at Neurology.org.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the article.

(CINRG-DNHS)[22] showed that participants were more often ambulatory at age 10 years and older if currently treated with GCs.[23] Here, we expand to a longitudinal time-to-event analysis of GC regimen effects on LoA.

Prescribed GC regimens are manifold in DMD,[24] but few studies have directly compared PRED vs DFZ.[11,20,25] There is evidence of better efficacy of daily GCs,[11] but several alternative regimens are applied (e.g., weekend,[26] 10-days-on/10-days-off[27]). A global, randomized, blinded trial of daily prednisone, daily DFZ, and 10-days-on/10-days-off prednisone is under way (www.for-dmd.org). In parallel, novel "dissociative steroids" aim to a broader therapeutic window by separating pharmacodynamic mechanisms responsible for efficacy and side effects.[28,29] Before randomized trial results and innovative treatments become available, natural history studies can provide useful information regarding different GC regimens in DMD.

METHODS

Standard protocol approvals, registrations, and patient consents. The institutional review board or ethics review board at each participating institution approved the study protocol, consent, and assent documents. Informed consent/assent was obtained for each participant before conducting study procedures.

Study population. We present data from 340 patients with DMD, aged 2 to 28 years, enrolled in the parent CINRG-DNHS (distinguished from a currently recruiting extension, http://clinicaltrials.gov/show/NCT00468832). Inclusion criteria have been described.[22]

GC treatment. At baseline and follow-up visits, we recorded time of beginning/discontinuation, drug, dose, and pattern of administration of previous and current GC regimens.

GC dose. Dose data were converted to ratios of recommended doses for PRED (0.75 mg/kg/d) and DFZ (0.9 mg/kg/d).

Definition of LoA. Age at LoA was defined by patient-reported continuous wheelchair use, confirmed by inability to walk 10 m unaided.[23,30]

Grouping by GC treatment relative to LoA. GC regimens <1 month were ignored. For comparisons of median LoA between GC-treated and untreated participants, we considered "GC-treated" only those patients who had been administered GCs for ≥1 year, starting ≥1 year before LoA, because a long-term effect cannot be attained with a short-term treatment.

Grouping by GC regimen for Kaplan–Meier analyses. Because of a low number of participants subject to intermittent regimens (10-days-on/10-days-off, 10 days/month, every other day, 5 days/week), we grouped these regimens together. We analyzed the high-dose (10 mg/kg/wk) 2 days/week ("weekend") regimen separately because of the pharmacologically different properties of this treatment.

Cox regression analyses of PRED and DFZ use, regimen, and dose. Because many participants changed drugs, regimen, and doses during treatment, all these variables were evaluated for concurrent effects as time-varying covariates in a Cox regression model, independent of grouping of individual participants (see also statistical analysis section below).

Overlap with CINRG clinical trials. Twenty-nine participants were transferred to the DNHS from a CINRG clinical trial of daily vs weekend prednisone.[26]

Side effects. We report frequency of physician-reported side effects in participants treated with GCs while ambulatory.

Classification of evidence. Primary research question: Does treatment with PRED or DFZ effectively delay LoA in DMD? This study provides Class IV evidence that GCs are effective in delaying LoA in patients with DMD.

Statistical analysis. Average GC dose was compared between drug-regimen subgroups using the Mann–Whitney U test, while cumulative dose and age at start of treatment were compared using Student t test. LoA was studied as event in a time-to-event model, with age as time variable, and censoring of ambulatory participants at the age of last follow-up. Median ages at LoA, calculated from empiric Kaplan–Meier curves, were compared using log-rank test. A Cox regression model was devised with the following time-varying covariates: GC drug (untreated, PRED, or DFZ), GC regimen (untreated, daily, low-dose intermittent, or weekend), and mg/kg/d dose, adjusting for random effects depending on CINRG study site. Hazard ratios (HRs) were calculated for each covariate, with untreated as reference (HR = 1) for categorical covariates. A linear test compared covariate levels within the Cox regression model. Statistical significance was set at $p < 0.05$. Frequency of adverse effects between regimens was compared by χ^2 test. STATA V13 (StataCorp, College Station, TX) and Partek GS 6.6 (Partek Inc., St. Louis, MO) were used for analyses.

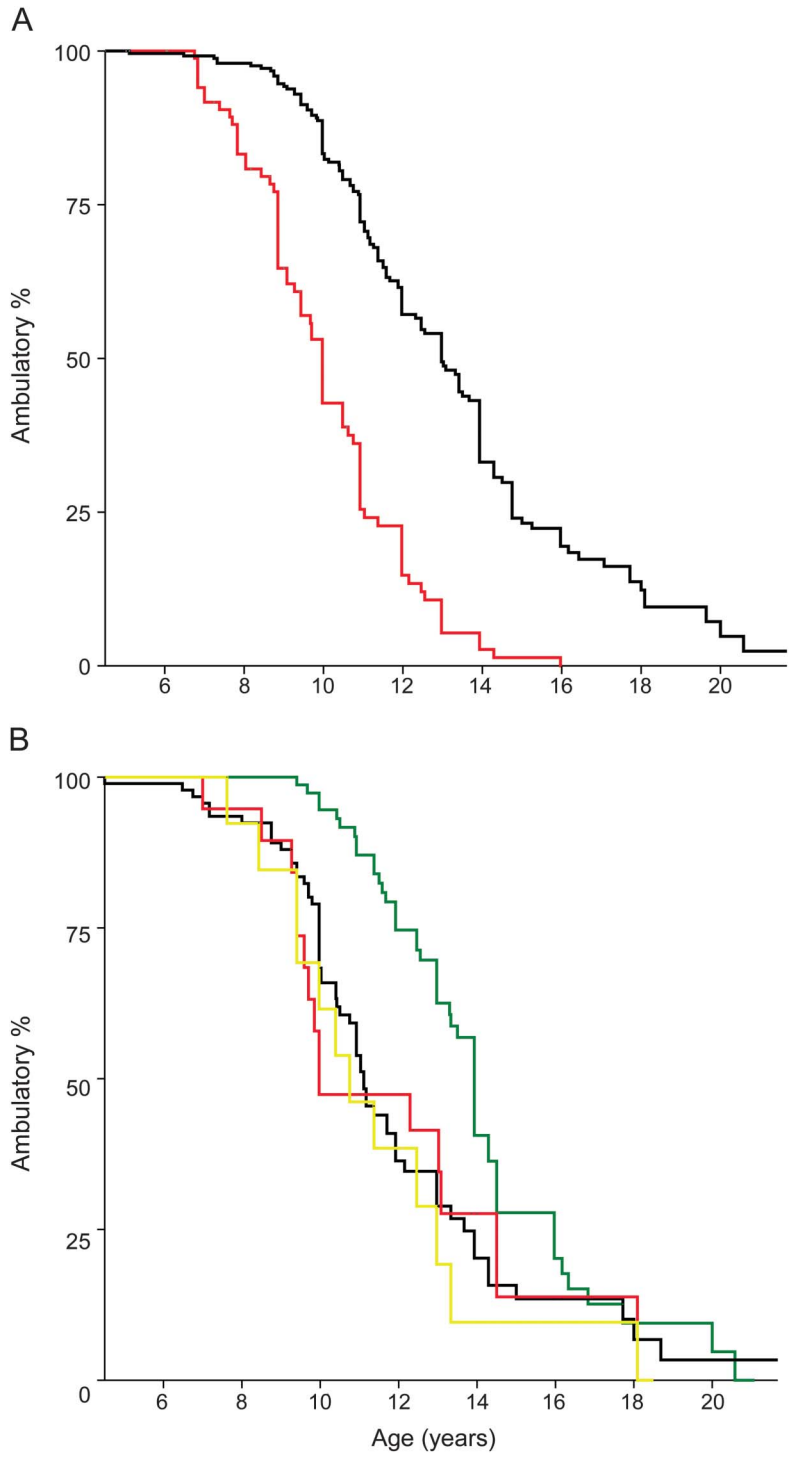
RESULTS

Age, follow-up, and ambulatory status. At last follow-up (data updated through December 2013), average age was 15.7 ± 5.6 years (range 4.5–33.1) and average follow-up 3.8 ± 1.8 years; 111 participants were ambulatory (32.6%) while 229 (67.4%) had lost ambulation. Average age at last follow-up was 11.2 ± 3.1 years in ambulatory participants and 18.0 ± 5.3 years in nonambulatory.

Distribution by GC treatment while ambulatory. Sixty-three participants (18.5%) were untreated while ambulatory (including one patient treated with a non-GC anabolic steroid). At last follow-up, 54 of these were nonambulatory, and 9 ambulatory and GC-naive. Conversely, 277 participants (81.4%) were treated with GCs while ambulatory. A ≥1 year GC treatment was administered while ambulatory to 252 participants (74.1% total, 91.0% treated). Average ± SD duration of treatment while ambulatory was 4.0 ± 3.3 years, ranging from 0.1 to 18.3 years.

GC treatment and age at baseline. Average age at baseline was higher in patients treated <1 year or untreated while ambulatory, vs treated ≥1 year while ambulatory (15.1 ± 6.4 vs 10.9 ± 5.2 years, $p < 0.001$), reflecting

Figure Kaplan-Meier plots of the proportion of ambulatory participants relative to age (years), grouped by glucocorticoid corticosteroid treatment



(A) Participants treated at least 1 year while ambulatory (n = 252, black line) vs participants treated less or untreated (n = 88, red line). (B) Participants treated with the most common drug-regimen combinations: daily PRED (n = 94, black line), high-dose 2 days/week PRED (n = 19, red line), low-dose intermittent PRED (n = 14, yellow line), and daily deflazacort (n = 80, green line). PRED = prednisone or prednisolone.

increased implementation of GC treatment as a standard of care in younger participants.

GC treatment and LoA. Kaplan–Meier analysis showed that median LoA was 3 years later in participants treated ≥1 year while ambulatory vs untreated or treated <1 year (13.0 vs 10.0 years, n = 252 vs 88, log-rank $p < 0.0001$; figure, A).

Distribution by GC regimen while ambulatory. As previously reported,[24] there was major variation in GC regimen prescription. Fourteen distinct regimens of PRED or DFZ were observed. PRED was administered while ambulatory to 150 participants (54.1% of treated) and DFZ to 91 (32.9%). Of 36 participants (13.0%) switching between drugs while ambulatory, 35 switched from PRED to DFZ (one later switching back to PRED) and one from DFZ to PRED. GCs were administered daily to 195 participants (70.4%), 2 days/week to 21 (7.6%), intermittently (including 10-days-on/10-days-off, 10 days/month, 5 days/week, every other day) to 14 (5.1%), and twice daily to one. Forty-six participants switched between regimens while ambulatory: 22 from nondaily to daily, 19 from daily to nondaily, and 5 between nondaily regimens (table 1).

Median LoA by regimen. The most frequently used treatment protocol (daily PRED, n = 94) was associated with a median age at LoA of 11.2 years (table 1). Median LoA was later in participants taking daily DFZ (13.9 years, n = 80, log-rank $p = 0.0001$), in those who switched from daily PRED to daily DFZ (14.0 years, n = 21, log-rank $p = 0.03$), and those who switched between different drugs and regimens (14.0 years, n = 15, log-rank $p = 0.009$). LoA in participants taking other regimens did not differ significantly from daily PRED. Kaplan–Meier plots of LoA for the most common regimens (daily PRED, daily DFZ, weekend PRED, and intermittent PRED) are shown in the figure, B. GC regimen frequencies at individual CINRG sites are shown in table e-1 on the *Neurology*® Web site at Neurology.org.

Dose. Average dose of daily PRED administered while ambulatory (n = 94) was 75% ± 17% of recommended, lower than daily DFZ (83% ± 15%, n = 80, $p = 0.002$) (table 1). Doses for weekend regimens (and switchers to-from weekend) were higher (see table 1) because of the different protocol (10 mg/kg/wk = 1.42 mg/kg/d).

Age at start of treatment. Average age at start of GC treatment (excluding treatments started after LoA) was 6.8 ± 2.1 years (range 2.0–14.2) (table 1). Daily PRED was started earlier than daily DFZ (6.6 ± 1.9 vs 7.2 ± 2.0 years, $p = 0.03$).

Time-varying Cox regression analysis of PRED vs DFZ, regimen, and dose. A Cox regression model was used to test concurrent, independent effects on LoA of several time-varying factors: use of PRED or DFZ; use of daily, low-dose intermittent, or high-dose weekend regimens; and average daily dose (table 2). The HR ± standard error (SE) associated with PRED

Table 1 Distribution by GC regimen administered while ambulatory, with average daily dose, average age at start of treatment, and median age at LoA for each regimen

Drug	Regimen	No. (%)	Dose[a] ± SD, %	Cumulative GC dose 1 = 1 y at PRED 0.75 or DFZ 0.9 mg/kg/d	Start age ± SD, y	Median age at LoA, y
PRED	Daily	94 (33.9)	75 ± 17	2.96	6.6 ± 1.9	11.2
DFZ	Daily	80 (28.9)	83 ± 15[b]	4.73[c]	7.2 ± 2.0[d]	13.9[c]
PRED	Switched	23 (8.3)	94 ± 37[d]	4.30[b]	7.0 ± 2.0	11.6
Switched	Daily	21 (7.6)	71 ± 16	3.87	6.2 ± 2.3	13.4[d]
PRED	High-dose 2 d/wk	19 (6.9)	131 ± 36[c]	5.64[c]	7.0 ± 2.1	10.0
Switched	Switched	15 (5.4)	85 ± 26	5.75[c]	5.2 ± 1.5	14.0[b]
DFZ	Switched	8 (2.9)	82 ± 14	3.64	6.2 ± 1.7	16.0
PRED	5 d/wk	5 (1.8)	71 ± 14	1.88	8.0 ± 1.1	10.7[e]
PRED	Every other day	4 (1.4)	38 ± 9	1.86	9.1 ± 1.9	10.7[e]
PRED	10 d on/off	2 (0.7)	47 ± 4	1.03	9.4 ± 0.4	10.7[e]
PRED	10 d/mo	2 (0.7)	50 ± 24	0.27	6.1 ± 0.4	10.7[e]
DFZ	High-dose 2 d/wk	2 (0.7)	136 ± 10	4.11	11.5 ± 2.9	—
DFZ	Every other day	1 (0.4)	65 ± 0	6.22	3.6 ± 0.0	—
PRED	Twice daily	1 (0.4)	48 ± 0	1.59	6.9 ± 0.0	—

Abbreviations: DFZ = deflazacort; GC = glucocorticoid corticosteroid; LoA = loss of ambulation; PRED = prednisone or prednisolone.
[a] Dose is indicated as % of standard mg/kg/d (0.75 mg/kg for PRED or 0.9 mg/kg for DFZ as applicable).
[b] The p value vs daily PRED $p < 0.01$.
[c] Log-rank test vs daily PRED $p < 0.001$.
[d] Log-rank test vs daily PRED $p < 0.05$.
[e] Data for grouped low-dose intermittent PRED regimens, log-rank p value vs daily PRED not significant.

was 0.498 ± 0.080 ($p < 0.001$). DFZ treatment was associated with a lower HR (later LoA) (0.294 ± 0.053, $p < 0.001$). The linear test between covariate levels indicated that this difference was statistically significant ($p = 0.003$). HRs for different administration regimens were 0.382 ± 0.058 for daily, 0.362 ± 0.119 for intermittent, and 0.508 ± 0.135 for high-dose 2 days/week. None of the differences between regimens was statistically significant in this model (few participants treated nondaily). HR for dose was 0.392 ± 0.070 ($p < 0.001$). Note that all Cox regression coefficients (table 2) are referred to as covariate effects (drug, regimen, or dose) in the

Table 2 Measures for the time-varying Cox regression analysis of effects of GC drugs, regimens, and dose on LoA

Levels of covariates	HR	SE	p Value	95% CI	Linear tests between covariate levels
Drug					PRED vs DFZ: $p = 0.003$[b]
Untreated	1[a]	—	—	—	
PRED	0.498	0.080	<0.001[b]	0.363–0.683	
DFZ	0.294	0.053	<0.001[b]	0.207–0.419	
Regimen					Daily vs 2 d/wk: $p = 0.27$; daily vs intermittent: $p = 0.86$; 2 d/wk vs intermittent: $p = 0.38$
Untreated	1[a]	—	—	—	
Daily	0.382	0.058	<0.001[b]	0.285–0.515	
2 d/wk	0.508	0.135	0.011[b]	0.301–0.856	
Intermittent	0.362	0.119	0.002[b]	0.190–0.689	
Dose, % of standard	0.392	0.070	<0.001[b]	0.277–0.553	—

Abbreviations: CI = confidence interval; DFZ = deflazacort; GC = glucocorticoid corticosteroid; HR = hazard ratio; LoA = loss of ambulation; PRED = prednisone or prednisolone; SE = standard error.
[a] Untreated was used as reference in the model (HR set at 1).
[b] Significant.

Table 3 Frequency of physician-reported side effects in participants treated with different GC regimens while ambulatory

Drug	Regimen	No.	Weight gain	Cushingoid	Behavior change	Growth delay	Cataracts	Low BMD or fracture	Skin abnormalities	Hirsutism	Stomach pain	Anxiety or depression	Gastric ulcer	Diabetes	Headache	Sleep disturbance	Hypertension
PRED	Daily	94	67	50	30	27	5	22	11	10	2	3	3	1	1	1	0
DFZ	Daily	80	63	72[a]	33	60[b]	29[b]	25	8	5	3	0	0	0	3	0	1
PRED	Switched	23	70	48	52[c]	17	4	9	13	0	4	0	0	4	0	0	0
Switched	Daily	21	76	62	52[c]	57[a]	14	24	24	0	0	0	10	0	0	0	0
PRED	High-dose 2 d/wk	19	79	37	42	5[c]	11	26	37[a]	0	0	0	0	0	0	5	0
Switched	Switched	15	80	67	73[c]	53[c]	40[b]	40	27	13	0	7	0	0	0	0	0
PRED	Low-dose intermittent[d]	13	23[a]	8[a]	15	8	0	23	8	8	8	8	0	8	0	0	0
DFZ	Switched	8	38	25	50	25	0	0	0	0	0	0	0	0	0	0	0
All	All	277[e]	65	55	37	37	15	22	13	6	2	2	2	1	1	1	0

Abbreviations: BMD = bone mass density; DFZ = deflazacort; GC = glucocorticoid corticosteroid; PRED = prednisone or prednisolone.
Data are percentages unless otherwise indicated.
[a] Chi-square p value <0.01 compared with daily PRED.
[b] Chi-square p value <0.001 compared with daily PRED.
[c] Chi-square p value <0.05 compared with daily PRED.
[d] Low-dose intermittent includes 10 days on/off, 10 days/month, 5 days/week, and every other day.
[e] All patients treated while ambulatory, not exactly equal to sum of other values because of a few patients on different, rarely prescribed regimens.

time-varying model, independent of grouping of individual participants by treatment (as in the Kaplan–Meier analyses); subsequently, data from "switcher" participants are included in Cox analyses. Also, the 1-year treatment threshold described above applies to log-rank tests of treated vs untreated, and not to Cox regression results described in this paragraph.

Frequency of side effects. Side-effect frequency was calculated in 277 participants (86.2%) with any treatment duration while ambulatory (table 3). Weight gain (65%), cushingoid appearance (55%), growth delay (37%), behavior changes (37%), low bone mass density and/or fracture (22%), cataracts (15%), and skin abnormalities (13%) were most frequently reported. Some frequencies might be underestimated because side effects were recorded for only the 3 most recent GC regimens before study baseline. We chose daily PRED, the most frequently prescribed regimen, as reference for comparisons. Weight gain frequency was similar for daily DFZ and daily PRED, but daily DFZ showed higher incidence of cushingoid appearance (72% vs 50%, $p = 0.002$), growth delay (60% vs 27%, $p < 0.0001$), and cataracts (29% vs 5%, $p < 0.0001$). Behavior changes were more common in switchers between different drugs (0.048), between different administration regimens ($p = 0.04$), or both ($p = 0.001$), suggesting that behavioral disturbances might often induce clinicians and families to modify the treatment. Reported growth delay was strikingly more frequent in switchers between drugs ($p = 0.006$ for daily treatment and $p = 0.03$ for others) but not in participants consistently on DFZ, confirming a strong association between DFZ and stunted growth. On the contrary, growth delay was rare (5% vs 27%, $p = 0.04$) with weekend GCs. Cataracts were also more frequent in switchers, but not in daily DFZ use ($p < 0.0001$). Skin abnormalities were more common with weekend GCs ($p = 0.004$). Finally, low-dose intermittent regimens showed a lower incidence of most side effects. This was statistically significant only for weight gain (23% vs 67%, $p = 0.002$) and cushingoid appearance (0.004), likely because of low numerosity in this group (n = 13).

DISCUSSION The long-term effect of GC treatment in prolonging independent ambulation in DMD, demonstrated by several previous studies,[9,19–21] is confirmed by data from the CINRG-DNHS presented here, with an estimated 3-year median delay of LoA. While virtually none of the untreated participants was able to walk beyond the age of 14 years, this was possible for approximately a third of GC-treated participants in the DNHS. However, because of inherent limitations of an observational, nonrandomized study, these estimates of GC effect

magnitude might be inflated. Recent years have seen a parallel increase in the frequency of GC prescription for DMD, and in the implementation of other standards of care such as physical therapy, management of joint contractures, and bone fracture prevention. In fact, CINRG-DNHS participants who did not receive GCs while ambulatory were significantly older on average than participants who did, denoting this "historical" improvement in care. It is not possible in an observational, nonrandomized study to clearly discern how much of the observed LoA delay is actually caused by GCs and how much by other treatments. Nevertheless, GC treatment was probably the single most important factor in this modification of the natural history of DMD.

PRED and DFZ regimens administered to CINRG-DNHS participants during the ambulatory phase of the disease were manifold, recapitulating a well-described variation in practice.[24] The recent observational study from the NorthStar Network[27] reported on a cohort of patients mostly treated with PRED, and compared daily and intermittent (mainly 10-days-on/10-days-off) regimens. The distribution of GC regimens was different in the CINRG-DNHS: a substantial part of the population was on DFZ, and daily regimens were preponderant.

Few studies have directly compared PRED and DFZ.[11] Based on these, the 2 drugs appeared comparable in efficacy but differed in tolerability.[25] Therefore, we did not anticipate our observations of a more than 2-year-later median age at LoA between participants treated with daily DFZ compared with daily PRED (Kaplan–Meier analysis) and a significant reduction of estimated yearly LoA risk with DFZ (Cox regression). This may be partly explained by higher average dosing in the DFZ group, in turn determined by more aggressive treatment, or, hypothetically, by a more favorable tolerability profile requiring less dose tapering. However, we did not observe a reduced incidence of weight gain with DFZ; in addition, most common side effects were more frequent, suggesting that clinicians prescribing DFZ used higher doses despite side effects and/or there was higher adherence to treatment. Earlier commencement of treatment, another hypothetical cause of increased efficacy, cannot explain the better outcome in DFZ-treated patients: on the contrary, daily PRED was started significantly earlier than daily DFZ in the CINRG-DNHS population. Because it is common in clinical practice to start treatment when motor function reaches a plateau, DFZ treatment may have been started later because of a later plateau of motor function, which denotes a milder disease progression. Furthermore, as many clinicians refrained from incrementing the dose with growth as a means of managing side effects, participants started younger on PRED may have received lower cumulative doses, because the starting dose, calculated on a lower weight, was left unchanged in subsequent years. In summary, there was a strong association of DFZ with later LoA in the CINRG-DNHS population, but this cannot be considered conclusive evidence for a greater long-term efficacy.

DFZ is not commercially available in the United States, where many CINRG sites are located, and it is more expensive than prednisone, implying that its use may have been associated with higher standards of care and possibly adherence. Nevertheless, it remains possible that DFZ possesses a greater long-term efficacy than PRED because of uncharacterized pharmacodynamic mechanisms that could not be ascertained by previous short-term studies. The results of the time-varying Cox regression analysis (adjusted for dose as an independent factor and for random effects of study site to account for standards of care) appear to support an independent beneficial effect of DFZ. Although the CINRG-DNHS was not specifically designed to compare standards of care between participant groups, we analyzed factors that might affect the clinical course such as orthopedic surgery and use of walking aids (table e-2). Indeed, participants receiving daily DFZ more frequently used ankle-foot/knee-ankle-foot orthoses or walkers, an indicated although not essential practice in DMD.[18] Data regarding physical therapy and night orthoses were scarce. We also excluded differences in genetic modifier polymorphism frequency in the *SPP1*[31,32] and *LTBP4*[33,34] genes (table e-2), which, as we recently reported, have a significant effect in this population.[35] Randomized clinical trials, such as FOR-DMD (Finding the Optimum Regimen for DMD), will shed more light on these issues. Until then, some consideration should be given to stratifying clinical trial cohorts by DFZ/PRED treatment.

Data regarding nondaily GC regimens in the CINRG-DNHS are complex to analyze because of their fragmentation and the common practice of switching regimens as a means of tapering or adapting doses. HRs for daily vs weekend regimens were not significantly different, consistent with findings of equivalence in quantitative muscle strength in a previous CINRG clinical trial.[26] However, low-dose intermittent regimens (e.g., 10-days-on/10-days-off) were seldom used within CINRG, so that a conclusive comparison between these and daily regimens, such as recently published by the NorthStar Clinical Network,[27] cannot be obtained from CINRG-DNHS data.

Two common side effects of chronic GC treatment in the pediatric population, cushingoid appearance and growth stunting, were significantly more frequent with daily DFZ than daily PRED. Again, this might be explained at least in part by higher

dosing or possibly adherence. The previously reported higher incidence of cataracts with DFZ[20] is confirmed by our data. However, we did not observe a lower frequency of weight increase with DFZ, as previously suggested,[25] although it is possible that if DFZ was dosed higher, a similar incidence of weight gain might still be the expression of better weight control with DFZ. Low-dose intermittent regimens (despite small participant numbers) showed lower frequencies of most side effects, as previously reported.[27] Except for less frequent growth stunting, the tolerability profile of weekend PRED appeared comparable to the daily regimen, as previously shown by a CINRG clinical trial.[26]

Consistent with comments following publication of GC treatment data from the NorthStar Network,[36–38] growth stunting appeared to be associated with later LoA. Indeed, patients treated with daily DFZ showed both the latest LoA and the most frequent growth stunting. It is difficult to discern from observational data whether a biomechanical advantage from short stature might have a causative role in delaying LoA or whether prolonged ambulation and short stature are simply concurrent effects of treatment. An answer to this question might be provided by systematic and longitudinal correlations of stature and functional measures (e.g., strength, speed). From a clinical standpoint, the greatest consideration should be given to the effect that stunted growth together with the frequently associated pubertal delay has on quality of life and self-image in patients with DMD, in an effort to tailor GC treatment to individual expectations and the needs of each patient.

In conclusion, we provide Class IV evidence that GCs are effective in delaying LoA in patients with DMD. The observation of better long-term outcome with DFZ might be partly attributable to higher dosing, higher adherence, and better standards of care. Nonetheless, stratification by PRED or DFZ treatment might be considered in clinical trials in order to account for variability of weakness progression. This study emphasizes the need for further randomized, blinded, longitudinal trials of different GC regimens in DMD.

AUTHOR CONTRIBUTIONS

L.B. contributed to study design, analyzed and interpreted data, and drafted the manuscript. H.G.-D. contributed to study design, performed statistical analyses, and critically revised the manuscript for intellectual content. L.P.M. contributed to study design, analyzed and interpreted data, and critically revised the manuscript for intellectual content. E.K.H. contributed to study design, analyzed and interpreted data, and critically revised the manuscript for intellectual content. T.D. contributed to study design, analyzed and interpreted data, and critically revised the manuscript for intellectual content. E.P.H. contributed to study design and critically revised the manuscript for intellectual content. A.C. contributed to study design, performed statistical analyses, and critically revised the manuscript for intellectual content. C.M.M. designed the study and critically revised the manuscript for intellectual content.

STUDY FUNDING

This project was funded through the Italian Ministry of Education PhD grant awarded to L.B. for the 28th Cycle of the Doctorate School of Medical, Clinical, and Experimental Science at the University of Padova, Italy; and grants from the NIH (U54HD053177, R24HD050846, UL1RR031988, UL1RR024992, U54RR026139, G12RR003051, 1R01AR061875, RO1AR062380), the US Department of Education/NIDRR (H133B031118, H133B090001), the US Department of Defense (W81XWH-09-1-0592).

DISCLOSURE

L. Bello, H. Gordish-Dressman, and L. Morgenroth report no disclosures relevant to the manuscript. E. Henricson reports grants from the US Department of Education/NIDRR, grants from US NIH/NIAMS, grants from US Department of Defense, and grants from Parent Project Muscular Dystrophy US during the conduct of the study; grants from Parent Project Muscular Dystrophy US, outside the submitted work; has served as a past member of the CINRG Executive Committee, and has worked as a paid consultant for PTC Therapeutics and Genzyme, Inc. T. Duong reports no disclosures relevant to the manuscript. E. Hoffman reports grants from NIH during the conduct of the study. A. Cnaan reports no disclosures relevant to the manuscript. C. McDonald reports grants from the US Department of Education/NIDRR, grants from US NIH/NIAMS, grants from the US Department of Defense, grants from Parent Project Muscular Dystrophy US during the conduct of the study; and grants from Parent Project Muscular Dystrophy US, outside the submitted work. Go to Neurology.org for full disclosures.

Received January 12, 2015. Accepted in final form May 22, 2015.

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