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Corticosteroid Treatments in Males With Duchenne Muscular Dystrophy: Treatment Duration and Time to Loss of Ambulation

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Abstract

This population-based study examines the association between corticosteroid treatment and time to loss of ambulation, stratifying by treatment duration (short: 0.25–3 years, long: >3 years), among 477 Duchenne muscular dystrophy cases identified by the Muscular Dystrophy Surveillance Tracking and Research Network (MDSTAR*net*). Those cases who received short-term corticosteroid treatment had a time to loss of ambulation that was 0.8 years shorter (*t* test) and an annual risk of losing ambulation 77% higher than the untreated (Cox regression). Conversely, cases who received long-term corticosteroid treatment had a time to loss of ambulation that was 2 years longer and an annual risk of losing ambulation 82% lower than the untreated, up to age 11 years; after which the risks were not statistically different. The relationship of corticosteroids and time to loss of ambulation is more complex than depicted by previous studies limited to treatment responders or subjects who lost ambulation during study follow-up.

Keywords

corticosteroid; Duchenne muscular dystrophy; ambulation; treatment duration

Duchenne muscular dystrophy is caused by a mutation in the dystrophin gene on the X-chromosome, and is the most common form of childhood-onset muscular dystrophy affecting approximately 1 in 3500 newborn boys.[1] Most patients with Duchenne muscular

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Author Contributions

KSK and DJF designed the study. KSK wrote the initial draft. KSK and KAC analyzed the data. KSK, KAC, DJF, DJM, and RV revised the manuscript and approved the final manuscript.

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Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

Each site has different approval numbers and the institutional review board approval was maintained at each site.

dystrophy exhibit signs of progressive muscle weakness before 6 years of age; around 13 years of age, individuals lose the ability to walk.[2,3] Later symptoms include contractures, scoliosis, and progressive impairment of respiratory and cardiac functions.[4,5] Individuals with Duchenne muscular dystrophy are expected to live to their middle 20s on average, and longer-term survival has been associated with timely and appropriate respiratory support.[6]

Duchenne muscular dystrophy is invariably progressive, and most pharmacologic treatments are aimed at delaying its progression by prolonging muscle strength. Though the exact mechanism is unknown, corticosteroids such as prednisone/prednisolone (prednisone) and deflazacort are associated with improved muscle strength and prolonged independent ambulation.[7–13] Deflazacort is preferred by some patients because it results in less weight gain than prednisone while having similar benefits.[4,14–18] The recommended dose for prednisone is 0.75 mg/kg/d, and for deflazacort, 0.90 mg/kg/d.[4,11,14,19–21] Prescription regimens are usually daily or intermittent (10 days on/10 days off).[22] A recent study has shown that daily treatment is more beneficial in prolonging ambulation than an intermittent dosing schedule.[23] However, the precise corticosteroid regimen that balances benefit and side effects, particularly in the long term, is still unknown and under investigation.[24] Randomized clinical trials on corticosteroid treatment have contributed some knowledge but have the disadvantage of short follow-up times. Retrospective trials have shown that patients with long-term corticosteroid treatment (5.5–8 years) can ambulate 2 to 5 years longer than those receiving no corticosteroids.[7–9,11] A long-term assessment of corticosteroid treatment and treatment duration is lacking.

Our objectives in this study are to describe corticosteroid treatment by medication type and treatment duration among boys affected by Duchenne muscular dystrophy using longitudinal, population-based surveillance data and to assess the association of corticosteroid treatment with time to loss of ambulation.

Methods

Study Population

MDSTAR*net* is the largest population-based surveillance program for individuals with Duchenne and Becker muscular dystrophy in the United States. It is a longitudinal observational surveillance project that includes individuals born between January 1982 and October 2011. The data were collected from 6 participating sites: Arizona, Colorado, Georgia, Hawaii, Iowa, and western New York State. For case ascertainment, neuromuscular clinicians from each site rigorously assigned each case into 1 of 5 diagnostic categories (definite, probable, possible, asymptomatic, or affected female) after reviewing data collected from clinical and diagnostic records by trained abstractors.[25] Details about the MDSTAR*net* methodology are presented elsewhere.[26]

From a total of 1054 cases, the sample size for this study included 477 males after applying the following exclusion criteria: (1) “affected female” cases, “possible” or “asymptomatic” cases (n = 136), (2) no data about mobility (n = 25), (3) existence of a comorbid condition (n = 19), (4) no mobility data available for patients ≥5 years old (n = 50), (5) inconsistent data (eg, indication of independent walking after ambulation loss, n = 50), and (6) likely cases of

a Becker phenotype (ie, walked after age 16 years or had first symptoms and signs of muscular weakness after age 6 years) (n = 200). Cases with corticosteroid treatment of less than 3 months were excluded as well (n = 27). To account for the negative correlation between treatment duration and age at initial treatment, we only included cases that initiated treatment between ages 5 and 10 years (n = 70 were excluded). The final sample of 477 boys came from 443 families because our data included 34 siblings.

Variables

Time to loss of ambulation, our primary outcome, was measured as time-to-event or follow-up time in years. Those who were still walking at their last clinic visit were right censored at that time. Treatment duration was set as the cumulative time treated (in years) prior to time to loss of ambulation. Cases were then categorized into 3 groups by this duration: short (0.25–3 years), long (>3 years), and untreated. Regarding type of corticosteroid medication, cases that exclusively used prednisone or deflazacort during the follow-up were assigned to the "prednisone" or "deflazacort" group, respectively. Individuals who took both medications at different times were assigned to the "multiple" group. Age at onset (of first sign or symptom) was defined as the age in years at which the first sign or symptom of muscle weakness occurred.

Statistical Analysis

We performed all data analyses in SAS 9.3.[27] To examine the association between corticosteroid treatment and time to loss of ambulation by treatment duration, for those who lost ambulation during the follow-up period, we applied a *t* test (equal or unequal variance as appropriate) to compare the mean time to loss of ambulation of the corticosteroid-treated cases by treatment duration (short, long) and medication type (prednisone, deflazacort, both) with the mean time for untreated. Next, we fitted a Cox proportional hazard model for the total sample, using follow-up time as the outcome variable and treatment duration (short/long/untreated) as an independent categorical variable. The untreated group was used as the reference category. As disease severity may differ among treatment groups, which may confound the association examined, age at onset was adjusted in the analysis. The proportional hazard assumption was checked by testing the significance of the interaction term between each treatment covariate (short/long) and the follow-up time in the model. In the *t* test, to account for potential correlations between siblings, we excluded younger siblings of the same family. In the Cox regression, we applied a marginal approach with a working independence assumption that adjusts for the outcome correlations by the robust sandwich estimate of Lin and Wei.[28]

Results

Corticosteroid Use

Fifty-four percent (n = 257) of 477 eligible cases were untreated. For cases treated with corticosteroids (n = 220), Table 1 shows corticosteroid use by medication type and treatment duration. Overall, 64.1% of the cases that received steroids took prednisone, 22.3% took deflazacort, and 13.6% received both medications at different time intervals. Overall, the mean age at initiation of treatment was age 7.0 years; by medication type, it was 7.1 years

for prednisone, and 6.8 years for deflazacort. The average duration of treatment prior to ambulation loss was 3.4 years (3.6 years for patients using deflazacort, 3.1 years for patients using prednisone). For the short-term treatment group, the mean age of treatment initiation was 7.3 years and the mean duration of treatment was 1.4 years (range 0.25–3.0 years); for the long-term treatment group, the mean age of treatment initiation was 6.8 years and the mean duration of treatment was 5.4 years (range 3.1–10.2 years).

Association Between Corticosteroids and Time to Loss of Ambulation

Table 2 displays the mean time to loss of ambulation of the oldest sibling in families by medication type and treatment duration, for cases that lost ambulation during follow-up. On average, untreated cases (n = 162) stopped walking at age 10.3 years. Cases in the short-term treatment group (n = 71) stopped walking 0.8 years earlier (at age 9.5 years), and cases in the long-term treatment group (n = 78) stopped walking 2 years later (at age 12.3 years). In both cases, the differences between treated and untreated were statistically significant ($P < .05$, *t* test). The boxplots in Figure 1 illustrates these time to loss of ambulation patterns.

Figure 2 illustrates the distribution of age at onset by treatment duration. Mean ages at onset were not statistically different in any pair of comparison of treatment duration (all *t* test $P > .05$). In the study samples, 71% (n = 338) of the cases lost the ability to ambulate; the remaining (n = 139) were right censored. In the check of proportional hazard assumption of the Cox model, the interaction of the covariate “long” and time to loss of ambulation was statistically significant. To deal with the violation of proportional hazard assumption, we transformed this “long” covariate into a time-dependent covariate with the form long * I (time ≤ c) and long * I (time > c), where c is the change point and I denotes the indicator function. The 2 coefficients for these covariates estimate the hazard ratio before and after a prefixed time (age) c. This c was estimated as the integer value that maximizes the partial likelihood of the fitted model in a grid search where the candidate values ranged from 5 to 16 by increments of 1. In our case, the estimated time (age) c was 11 years of age.

In Table 3, the risk of ambulation loss adjusting for age at onset was about 77% higher for the short term treated than that of the untreated group ($P < .001$). On the other hand, the risk of ambulation loss for the long-term treated was 82% lower than that of the untreated by age 11 years or younger ($P < .001$). After age 11 years, the difference was not statistically significant ($P = .47$), possibly due to lack of statistical power in this age group. Age at onset was not significantly associated with time to loss of ambulation ($P = .77$).

Discussion

The apparent inverse association between short-term steroid use and time to loss of ambulation was unexpected; any steroid use would be assumed to provide therapeutic benefits for prolonging ambulation compared to no treatment. It is possible that individuals with short-term steroid use discontinued their treatment earlier than intended because the treatment may not have helped to maintain muscle strength. Alternatively, these individuals may have begun steroid treatment at the age when a rapid decline in muscle strength was noted, which is suggested by the observation that on average they initiated steroids 6 months later than the long-term treatment group. Another explanation could be that these individuals

may have experienced more serious side effects, which may imply that they were more likely to be nonresponders to the treatment.

Several Duchenne muscular dystrophy studies with small sample sizes have reported time to loss of ambulation as the primary outcome[9,12,29,30]: One study compared males treated with deflazacort (n = 17) to untreated males (n = 11) and found that the treated walked 1.3 years longer after a 2-year follow-up. However, those still walking at the end of follow-up were not included in the analyses.[12] In another study, Pradhan et al[29] found that ambulation was prolonged for about 3 years among males (n = 15) who were treated with prednisolone when compared to an untreated group (n = 19), but the ambulation gain was assessed only for those who tolerated the corticosteroid therapy (0.75 mg/kd/d) with fewer side effects and showed immediate improvement in muscle power after 6 months of treatment. In a recent retrospective study, King et al[9] reported that Duchenne muscular dystrophy males treated with corticosteroid for at least 1 year (n = 75) ambulated 3.3 years longer than untreated males (n = 68). All of these studies only included cases that had ceased ambulating when the mean time to loss of ambulation was compared between the corticosteroid-treated and the untreated group with a wide variation in treatment duration. This analytical scheme, which ignores censored cases or potential non-responders to the treatment, might lead to imprecise estimates of association between corticosteroid treatment and time to loss of ambulation by subsampling.

Our study has several limitations. First, it is observational. Multicenter randomized clinical trials with long-follow up times, however, are rare because of cost and time constraints. The importance of large observational studies with a robust design can be a valuable tool to guide future trials and their importance has been acknowledged.[30–33] Second, we focused on the association of corticosteroid treatment with loss of ambulation, but this relationship should be weighed against the side effects. Third, it was not possible to understand if attention to other details (ie, stretching, contracture release, etc) may have impacted duration of ambulation. Fourth, inclusion of genetic modifiers on disease progression in Duchenne muscular dystrophy such as Osteopontin or LTBP4 genotype, if such data were available, would increase the precision of the association examined in our study.[34,35]

Conclusions

In conclusion, we found that the short term treated with corticosteroid was overall negatively associated with time to loss of ambulation, and the long term treated was positively associated with time to loss of ambulation at an earlier stage of treatment. While Corticosteroid treatment will continue to be valuable for Duchenne muscular dystrophy cases until alternative treatments are discovered, further assessments of the association of this therapy with time to loss of ambulation are still warranted.

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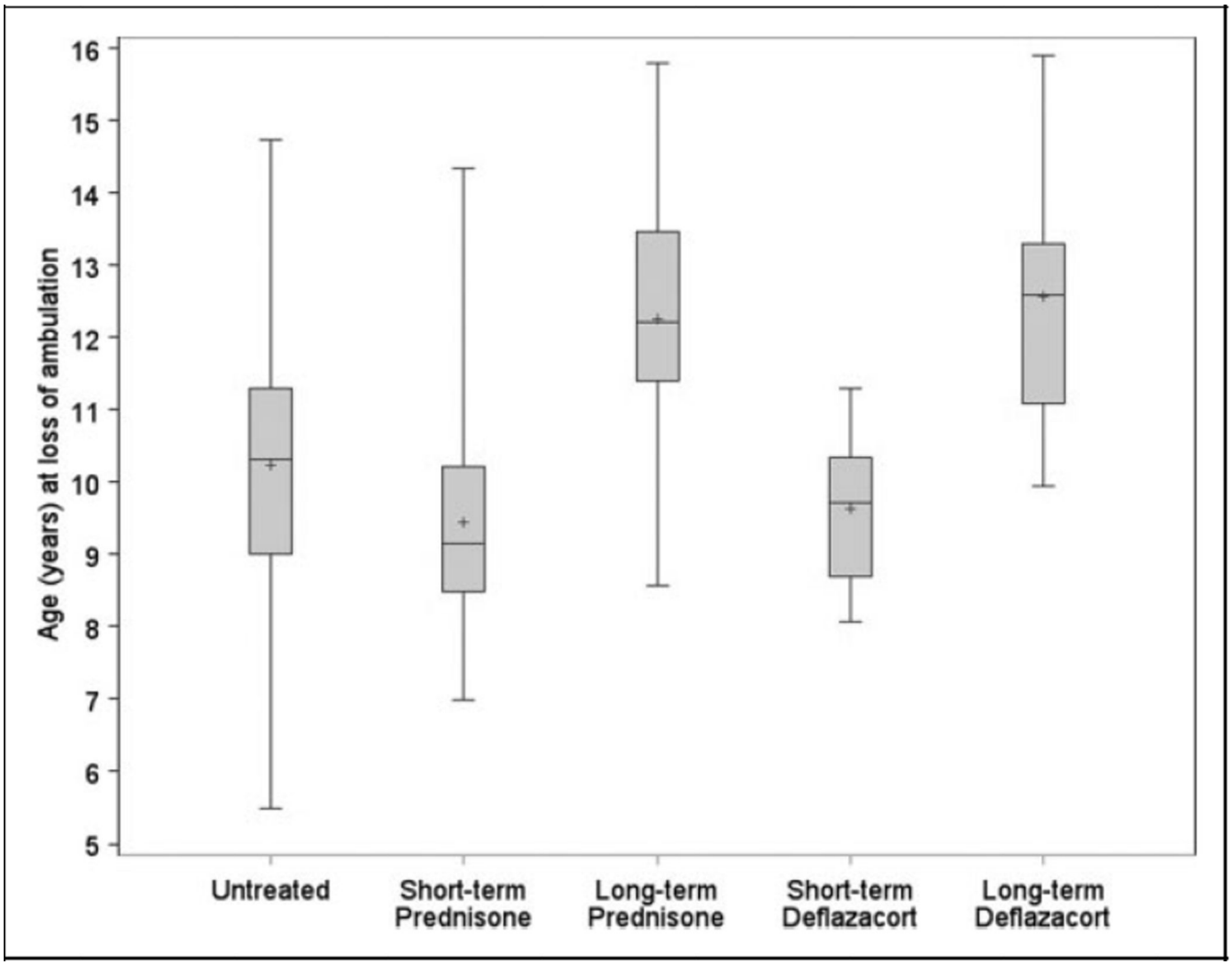

Figure 1.
Boxplots of the distribution of time to ambulation loss (years) by medication and treatment duration.

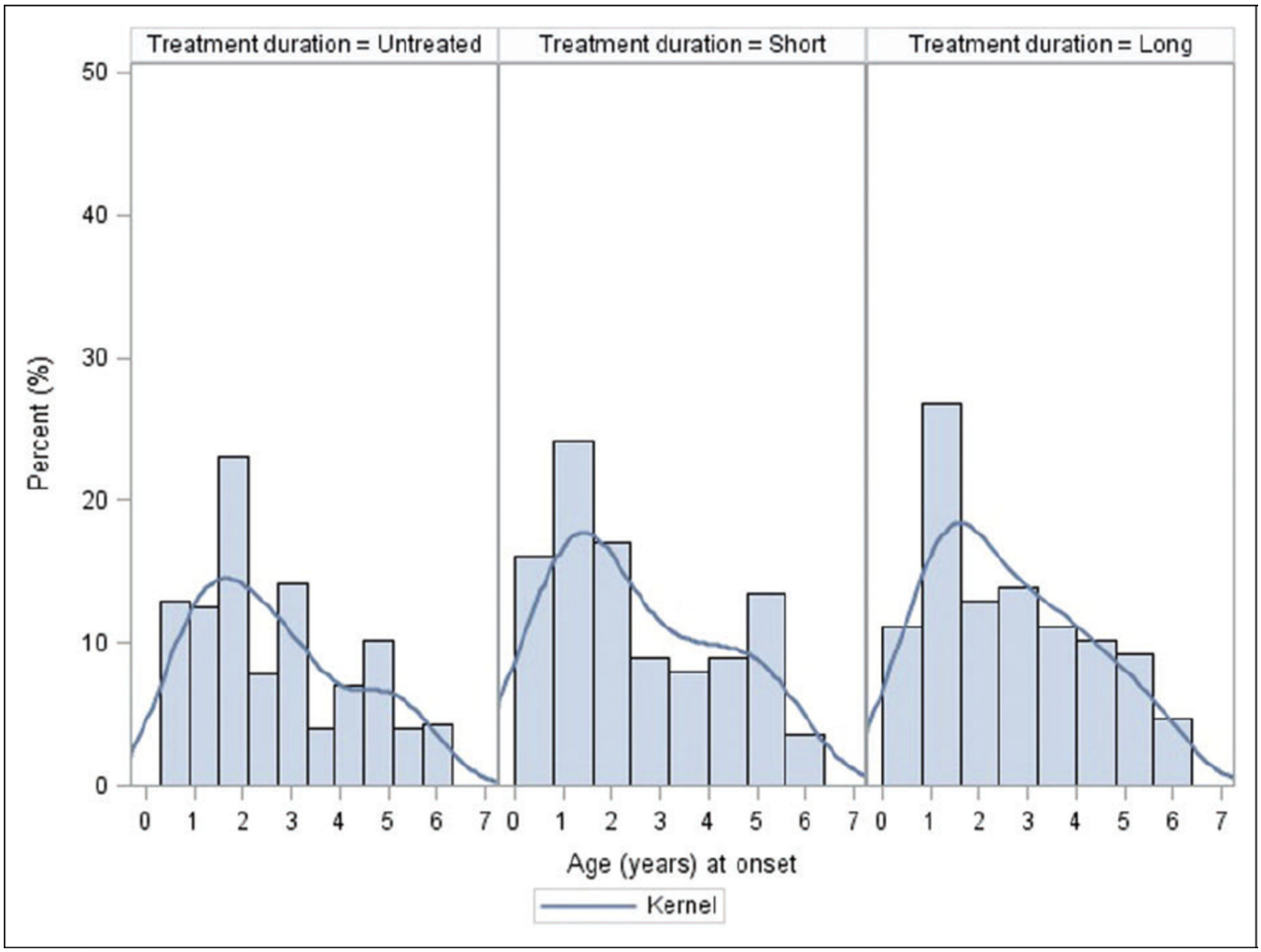

Figure 2.
Distribution of age at onset (years) by treatment duration.

Table 1

Corticosteroid Use by Medication Type and Treatment Duration.[a]

	Medication			
Treatment duration	**Prednisone**	**Deflazacort**	**Multiple**	**Overall**
Untreated, n	–	–	–	257
Short (3 mo–3 y), n (%)	78 (69.6)	25 (22.3)	9 (8.0)	112
Age at initiation (y)	7.3 ± 0.1	7.0 ± 0.2	7.4 ± 0.5	7.3 ± 0.1
Treatment period (y)	1.3 ± 0.1	1.7 ± 0.1	1.8 ± 0.3	1.4 ± 0.1
Long (>3 y), n (%)	63 (58.3)	24 (22.2)	21 (19.4)	108
Age at initiation (y)	6.7 ± 0.1	6.7 ± 0.2	6.9 ± 0.3	6.8 ± 0.1
Treatment period (y)	5.4 ± 0.2	5.5 ± 0.4	5.2 ± 0.4	5.4 ± 0.2
Overall (≥3 mo), n (%)	141 (64.1)	49 (22.3)	30 (13.6)	220
Age at initiation (y)	7.1 ± 0.1	6.8 ± 0.2	7.0 ± 0.2	7.0 ± 0.1
Treatment period (y)	3.1 ± 0.2	3.6 ± 0.3	4.2 ± 0.4	3.4 ± 0.2

[a] Values are mean ± standard error unless otherwise noted.

Table 2

Mean (SE) Age at Time to Loss of Ambulation by Medication Type and Treatment Duration, Excluding Younger Siblings.

	Medication			
Treatment duration	**Prednisone**	**Deflazacort**	**Multiple**	**Overall**
Untreated, n	–	–	–	162
Age at TLA, mean (SE)				10.3 (0.1)
Short, n	55	12	4	71
Age at TLA, mean (SE)	9.4 (0.2)[a]	9.6 (0.3)[a]	10.9 (0.7)	9.5 (0.2)[a]
Long, n	51	11	16	78
Age at TLA, mean (SE)	12.3 (0.2)[a]	12.6 (0.6)[a]	12.0 (0.3)[a]	12.3 (0.2)[a]

Abbreviation: SE, standard error; TLA, time to loss of ambulation

[a]Significantly different ($P < .05$) compared to the untreated.

Table 3

Hazard Ratios (HRs) for Loss of Ambulation for the Total Sample.

Covariates	HR (95% CI)	*P* value
Untreated	Referent	
Short	1.77 (1.34, 2.32)	<.001
Long		
≤Age 11 y	0.18 (0.10, 0.29)	<.001
>Age 11 y	0.88 (0.62, 1.25)	.47
Age at onset	1.00 (0.95, 1.08)	.77

Abbreviation: CI, confidence interval.