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Associations between timing of corticosteroid treatment initiation and clinical outcomes in Duchenne muscular dystrophy

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Abstract

The long-term efficacy of corticosteroid treatment and timing of treatment initiation among Duchenne muscular dystrophy (DMD) patients is not well-understood. We used data from a longitudinal, population-based DMD surveillance program to examine associations between timing of treatment initiation (early childhood [before or at age 5 years], late childhood [after age 5 years], and naïve [not treated]) and five clinical outcomes (age at loss of ambulation; ages at onset of cardiomyopathy, scoliosis, and first fracture; and pulmonary function). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated using survival analysis. DMD patients who initiated corticosteroid treatment in early childhood had a higher risk of earlier onset cardiomyopathy compared to cases who initiated treatment in late childhood (HR = 2.0, 95% CI = [1.2, 3.4]) or treatment naïve patients (HR = 1.9, 95% CI = [1.1, 3.2]), and higher risk of suffering a fracture (HR = 2.3, 95% CI = [1.4, 3.7] and HR = 2.6, 95% CI = [1.6, 4.2], respectively). Patients with early childhood treatment had slightly decreased respiratory function compared with those with late childhood treatment. Ages at loss of ambulation or scoliosis diagnosis did not differ statistically among treatment groups. We caution that the results from our study are subject to several limitations, as they were based on data abstracted from medical records. Further investigations using improved reporting of disease onset and outcomes are warranted to obtain a

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more definitive assessment of the association between the timing of corticosteroid treatment and disease severity.

Keywords

Duchenne muscular dystrophy; Corticosteroid; Ambulation; Cardiomyopathy; Scoliosis; Fractures; Pulmonary function

1. Introduction

Duchenne muscular dystrophy (DMD) is an inherited childhood-onset dystrophinopathy characterized by mutations in the *DMD* gene that leads to progressive muscle weakness. Most individuals with DMD lose their ability to walk by age 13 years [1,2]. In 2010, the prevalence of DMD was estimated at approximately 1.4 per 10,000 males aged 5 to 9 years and 1.02 per 10,000 males aged 5 to 24 years in several U.S. sites [3]. Currently, individuals with DMD are expected to survive beyond their teen years, as pharmacological treatment and clinical advances in cardiac and respiratory care have extended survival of affected individuals into their early 30s [4,5].

Most pharmacological treatments for DMD are aimed at delaying its progression by delaying onset of specific morbidities and prolonging muscle strength. At present, corticosteroids and angiotensin-converting enzyme (ACE) inhibitors are the most commonly prescribed treatments that have been reported to modify disease progression in individuals with DMD. Corticosteroids have been observed to improve or maintain muscle strength resulting in prolonged independent ambulation [6–13], a delay in cardiomyopathy onset or preservation of cardiac function [14–18], and preservation of pulmonary function [6,19–22], compared to untreated or natural history DMD controls. Early treatment (in children aged 9.5 to 13 years) with the ACE inhibitor, perindopril, has been observed to delay onset and progression of left ventricle dysfunction in individuals with DMD [23,24].

Despite the reported therapeutic effects of corticosteroids, the long-term benefits and risks associated with their use are unclear, and there are no generally accepted guidelines for the timing of treatment initiation [25–29]. A few studies have observed that corticosteroids initiated before age 5 years preserved respiratory function [30], prolonged ambulatory function [9], and contributed to remission of clinical symptoms [31,32] in individuals with DMD. These findings should be interpreted with caution because these studies lacked sufficient statistical power due to limited sample sizes (fewer than 5 patients) and lacked comparison groups of patients who began treatment at later ages or were untreated [9,30–32]. Moreover, some of these studies had follow-up periods (five years or less) [31,32] that were too short to evaluate long-term functional outcomes. As a result, the long-term effectiveness of corticosteroid treatment by timing of initiation, particularly in early childhood, has not been well-studied. A large-scale study with an extended follow-up period and a control group of affected individuals without corticosteroid treatment is needed to examine the associations between timing of treatment initiation and clinical outcomes in DMD. To address this need, we examined associations between corticosteroid treatment and timing of treatment initiation and five clinical outcomes – age at loss of ambulation; ages at

onset of cardiomyopathy, scoliosis, and first fractures; and pulmonary function among males with DMD from the population-based Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STAR*net*).

2. Methods

2.1. Study population

Established in 2002 by the Centers for Disease Control and Prevention (CDC), the MD STAR*net* is a population-based surveillance program that retrospectively identified and prospectively followed cases with Duchenne and Becker muscular dystrophies (DBMD), who were born from January 1, 1982 through December 31, 2011, diagnosed by age 21 years, and resided following diagnosis in one of six surveillance sites. Starting in 2004, Arizona, Colorado, Iowa, and western New York State began collecting data. Georgia joined the MD STAR*net* in 2006 and Hawaii in 2008. All cases were followed up for a minimum of 1 year following identification. Arizona and Hawaii obtained institutional review board approval to ascertain cases with DBMD from multiple sources, such as hospital records, neuromuscular clinics, and birth defect surveillance programs. The remainder of sites amended existing state codes for public health surveillance of birth defects to make DBMD reportable conditions. Clinical data abstracted from medical records for each potential case were reviewed by a committee of neuromuscular physicians to assign a case definition of: definite, probable, possible, asymptomatic, or affected female [33]. ‘Definite’ cases had the documented clinical symptoms referable to a dystrophinopathy and direct support of the diagnosis by at least one of the following criteria: 1) DNA analysis demonstrating a dystrophin mutation; 2) muscle biopsy demonstrating abnormal dystrophin; or 3) elevated creatine kinase, X-linked pedigree, and an affected family member meeting one of the above 2 criteria. ‘Probable’ cases lacked the DNA analysis data to meet the definition of definite cases. ‘Possible’ and ‘asymptomatic’ cases lacked further data required to meet criteria for definite case. More details of MDSTAR*net* surveillance methods have been published elsewhere [3,33,34].

Out of the 1054 cases identified by the MD STAR*net*, 918 males were assigned a definite or probable case definition. Age at onset of the first signs and symptoms was used to identify DMD cases, which was defined as onset of symptoms prior to the 6th birthday. Of the 918 cases, 192 were excluded due to onset of first signs and symptoms documented in the medical record after the 6th birthday: a mobility issue including trouble rising/walking/running/jumping, frequent falling/clumsy, Gower sign, gross motor delay, muscle weakness, or abnormal gait, which were used as a proxy for Becker muscular dystrophy. The final analytic dataset included 726 cases from 660 families. Among patients treated with steroid in our analytic sample, only those who had been treated for 6 or more months before developing a given outcome or before being right censored were considered for further analysis. Therefore, the analytical sample sizes varied from 481 to 666 cases for four clinical outcomes examined: age at loss of ambulation and ages at onset of cardiomyopathy, scoliosis, and first fractures (Table 1); data for 255 cases were available for pulmonary function analysis.

2.2. Clinical outcomes

Age at loss of ambulation was defined as the age in years at which ‘ambulation ceased’ or ‘fulltime wheel chair use’ was identified as first documented in medical records available for abstraction.

Age at cardiomyopathy onset was defined using standard measures of a diagnosis of cardiomyopathy [14,35–38]: a shortening fraction (SF) < 28%, an ejection fraction (EF) < 55% if SF was not available, or a calculated SF < 28% based on M-Mode data of left ventricular end diastolic and end systolic dimensions when both SF and EF were not available.

Age at first diagnosis of scoliosis was defined as the age in years at the first report of spinal curvature >30° as measured by lumbar X-rays in medical records available for abstraction, or age in years of the first documented scoliosis surgery when X-ray records were unavailable.

Age at first fracture was defined as the age in years of the first fracture, regardless of site, experienced by a DMD case. The fracture sites recorded in our data and ordered by diminishing frequency were femur, tibia/fibula, humerus, spine, ankle, arm, leg, foot, clavicle, and wrist.

Forced vital capacity (FVC) values in liters (L) that met pulmonary function test (PFT) quality according to the American Thoracic Society (ATS)/European Respiratory Society 2005 guidelines: ‘ATS criteria’, ‘good quality/effort’, or ‘repeatable’ (at least 3 FVCs: 2 largest within 0.15 L; if FVC < 1.00 L, then within 0.10L) were used for analysis. Unlike the other four clinical outcomes examined, we extracted repeated FVC values, where available, and applied a different method for analysis as explained in the following section.

2.3. Classification of DMD cases by timing of corticosteroid initiation

Cases were classified into three treatment groups according to the use of corticosteroid treatment and the timing of treatment initiation. Cases without documentation of being prescribed corticosteroids were assigned to the corticosteroid naïve group; cases that initiated corticosteroid treatment (deflazacort, prednisone, or prednisolone) before or at 5 years of age were assigned to the early childhood treatment group; and cases that initiated treatment after age 5 years were assigned to the late childhood treatment group. We set the minimum duration for treatment as a 6-month interval at any time prior to the occurrence of a clinical outcome examined (age at loss of ambulation; ages at onset of cardiomyopathy, scoliosis, and first fracture). Setting treatment duration at 6 months or more allowed assessment of the effect of longer-term corticosteroid treatment, which was the focus of this investigation. Because of the repeated outcomes used for the PFT analysis, cases with a minimum duration of 6 months of corticosteroid treatment prior to the initiation of the first PFT were included in our analyses.

2.4. Statistical analysis

For the onset of loss of ambulation, cardiomyopathy, scoliosis, or first fracture, we used Kaplan–Meier (KM) estimates to describe overall time to event and estimate the median age

(95% confidence interval, CI) at onset of each event by treatment group. We used Cox proportional hazard models to estimate associations between the age at clinical outcome and each treatment group (naïve, early childhood, and late childhood). For cases that did not show loss of ambulation, cardiomyopathy, or scoliosis by the end of the study period, we calculated two different right censored ages: age at their last recorded clinical test and age at last clinic visit. These analyses permitted us to examine the impact of right censoring on the results of cases who were followed but were never prescribed the relevant clinical test during the study period. Because a fracture was recorded when it occurred, cases without fractures were right censored only at the age of their last clinic visit. Analyses were repeated for each type of right censored age defined. We detected hazard rate differences for each pair of treatment groups (early vs naïve, early vs late, late vs naïve) using the Wald test. To account for possible outcome correlations among siblings, we used a robust sandwich estimator to estimate the covariance matrix [39]. Because cases who received treatment at an earlier age were likely to have an earlier age at onset of first signs or symptoms, disease severity may have differed among the treatment groups (e.g., overall, for the more severe cases in the early treatment group, the mean age at onset of first signs and symptoms for naïve, early, and late childhood treatment groups were 2.5, 2.1, and 2.7 years respectively), which may confound the associations estimated. Thus, we adjusted for age at onset of first sign or symptoms in all analyses as a continuous variable as a proxy for disease severity. Because of the potential for longer treatment duration among cases who started early compared to those who started late and the potential impact of treatment duration on clinical outcomes, we tested the difference in treatment duration among the early and late childhood treatment groups prior to applying Cox regression analysis. Also, in the Cox regression model for the analysis of the onset of cardiomyopathy, any use of cardiac medications prior to cardiomyopathy onset was included in the models and adjusted as a dummy variable. The names of medications (110 in total) used to treat cardiomyopathy were obtained from the American Heart Association and were matched to medications recorded in the surveillance database. We excluded reports of antiplatelet agents, anticoagulants, and statins [40].

Lastly, a linear regression was applied to estimate the expected difference of absolute FVC values between each pair of treatment groups examined, adjusting for age in years at each PFT along with age in years at onset of symptoms and signs. Because cases had repeated FVC values over time, the correlations among the repeated measurements were considered using a generalized estimating equation with a first-order autoregressive covariance structure. All analyses were done in SAS version 9.3 (SAS Institute, Cary, NC). In all analyses we considered for multiple testing using the Bonferroni correction; P-value $\leq 0.02 \approx 0.05/3$ was only treated statistically significant. We also conducted sensitivity analyses for all outcomes by excluding younger siblings from each family to examine the impact that the presence of an older affected sibling may have had on treatment initiation in younger siblings.

3. Results

Of the 726 cases in our analyses, 182 (25.1%) were abstracted from Georgia, followed by Arizona (23.8%), Colorado (21.1%), western NY (14.2%), Iowa (13.6%), and Hawaii (2.2%). By race/ethnicity, we had 437 (60.2%) cases who were non-Hispanic white, 148

(20.4%) Hispanic cases, 87 (12.0%) other race/ethnicity, and 54 (7.4%) with race/ethnicity missing. By corticosteroid treatment and timing of treatment initiation, 343 (47.3%, 301 definite and 42 probable) cases were corticosteroid treatment naïve, 67 (9.2%, 66 definite and 1 probable) initiated treatment in early childhood, and 316 (43.5%, 296 definite and 20 probable) initiated treatment in late childhood. Compared to cases in the late childhood treatment group, on average, those in the early childhood treatment group began treatment 3.4 years earlier (age 4.2 vs 7.6 years, $p < 0.001$). The mean duration of corticosteroid treatment prior to each clinical outcome examined ranged from 5.9 to 6.4 years. For all outcomes, no statistical difference in treatment duration was found between the early and late childhood treatment groups (all $p > 0.05$, t-test) prior to the occurrence of any clinical outcome (data not shown).

When the right-censoring age was set at the last available clinical test record, the median age at which cases had a 50% chance of being ambulatory was estimated at 11.1 years for those who were treatment naïve, 13.2 years for those in the early childhood treatment group, and 12.5 years for those in the late childhood treatment group (Table 1). For cardiomyopathy and scoliosis, the median ages free from each outcome were the greatest for cases in the late childhood treatment and naïve group (18.0 and 15.2 years respectively). When the right-censoring age was set at the last clinic visit, as expected, the sample size was larger and the corresponding median ages tended to be slightly older for each treatment group due to the later time at which the cases were censored (Table 1). The median age free from the first fracture was estimated as the highest (19.6 years) in the late childhood treatment group. Overall survival rates by treatment group are presented in KM curves in Fig. 1.

In the Cox regression models adjusted for age at onset of first signs or symptoms (and cardiac medication use for the analysis of cardiomyopathy onset), the risk of cardiomyopathy and first fracture onset was significantly higher for cases in the early childhood treatment group compared to either those in the treatment naïve or the late childhood treatment groups (Table 2). When right censoring cases at last available clinical test record, the risk of cardiomyopathy onset among cases in the early childhood treatment group was 1.9 times as high as (95% CI = 1.1–3.2, P = 0.02) the risk for those in the treatment naïve group and 2.0 times as high as (95% CI = 1.2–3.4, P = 0.01) the risk for those in the late childhood treatment group. The hazard ratios (HRs) were comparable when the analyses were repeated using age at the last clinic visit for right censoring. Also, the risk for first fracture among cases in the early childhood treatment group was 2.6 times as high as (95% CI = 1.6–4.2, P < 0.01) the risk for those in the treatment naïve group and 2.3 times as high as (95% CI = 1.4–3.7, P < 0.01) the risk for those in the late childhood treatment group. No significant differences were observed between the late childhood treatment group and the treatment naïve group for onset of cardiomyopathy and first fracture. For loss of ambulation or onset of scoliosis, no significant associations were observed for the pairwise comparisons between treatment groups when right censoring cases at either age at last available clinic test record or age at last clinic visit.

Among the 726 cases analyzed, PFTs met the inclusion criteria in 255 (35.1%) cases with a total collection of 1030 absolute FVC values. Adjusting for age at onset of first sign or symptoms and age at each test in the linear regression model, the expected FVC value for

cases in the early childhood treatment were 0.39 L lower ($P < 0.01$) than the values for those in the late childhood treatment group (Table 3). No significant difference was observed for other pairs of groups ($P > 0.02$). For all analyses conducted, removal of younger siblings did not appreciably change the estimates observed from inclusion of all eligible cases in the analyses (data not shown).

4. Discussion

By analyzing the longitudinal, population-based data from the MD STAR*net*, we observed that DMD cases who initiated corticosteroid treatment early (age ≤5 years) were more likely to have earlier onsets of cardiomyopathy and first fracture compared with those who initiated treatment in late childhood (age >5 years) or those who were treatment naïve. Patients who initiated treatment early also showed overall decreased respiratory function compared with the patients in the late childhood treatment group. For all outcomes examined, no statistically significant differences were observed between the treatment naïve group and late childhood groups.

A recent 14-year follow-up study of 8 boys who received early childhood treatment with corticosteroids (ages 2–4 years) reported that such treatment preserved pulmonary and cardiac function for 4 of the boys [9]. Of these 4 boys with preserved pulmonary and cardiac function, FVCs were also normal in 2 boys and mildly reduced in the other 2 boys; left ventricular EF was normal in 3 boys at their last follow-up (ages 16–18 years). By comparison, the 4 boys in the study without preserved pulmonary and cardiac function were reported to have lost ambulation or the ability to rise before age 10 years. Other investigations have indicated the potential benefits of corticosteroid treatment on cardiac function [7,14,17], but not consistently [41,42]. Using MD STAR*net* data, Barber et al. reported a delayed onset of cardiomyopathy among corticosteroid users, compared to the naïve group [14]. This finding appears to be inconsistent with the present study. A key difference is that in the present study the corticosteroid treated patients were separated into early treated and late treated; whereas these two groups were combined into a single treatment group in Barber et al. Of note, in the present study the risk of cardiomyopathy onset among those aged about 12 to 18 years was estimated lower in the late treatment group compared to the treatment naïve group, but this difference did not reach statistical significance in the period of the study. Inverse associations of corticosteroid treatment with fractures [6,8] and scoliosis [8,43] in DMD, relative to untreated boys, have been reported previously; however, in these efficacy studies, the start of corticosteroid was either unknown or it was later than age 6 years. It is possible that the lower FVC in early treated cases reflects greater total body growth suppression from longer and/or early steroid treatment. However, we do not have enough data to compare growth among the cases who were treatment naïve vs the other treated groups.

In this study we simply assessed the potentially adverse relation between morbidity and timing of corticosteroid treatment initiation. Because this is an observational study, we cannot conclude that early treatment resulted in poorer clinical symptoms. A randomized clinical trial would be the definitive method to address this issue; however, given the progressive nature of DMD, we can anticipate that the efficacy of early treatment may alter

the natural history to the point that it becomes comparable to the progression observed among those with a presumed less severe phenotype (i.e., late childhood treatment or treatment naïve groups).

The relatively severe phenotype or rapid disease progression, such as the one possibly present in the early childhood treatment group, may lead to a higher risk of developing cardiomyopathy, suffering fractures, or decreasing pulmonary function compared to cases without this phenotype. To account for this possibility, we controlled for age at onset of first signs and symptoms as a proxy for disease severity across treatment groups. Interestingly, we observed no statistical difference of clinical symptoms examined between the cases in the treatment naïve and late childhood treatment groups. It is possible that the comparable disease severity in the two groups with corticosteroid treatment (age 2.1 and 2.7 years for age at onset of first signs and symptoms for early and late treated groups, respectively) was not altered by the treatment in one group, or our data did not have enough statistical power to detect such a difference. However, lack of statistical significance does not mean lack of clinical significance.

To our knowledge, this is the first large-scale study examining the associations between corticosteroid treatment and timing of initiation with several clinical outcomes in the same study population. These clinical outcomes often have been included in DMD studies related to the efficacy of corticosteroid treatment, but have been reported separately. Variations of study population and study designs can hinder the synthesis of findings regarding the effect of corticosteroid treatment on clinical outcomes. Although the evaluation of multiple clinical outcomes in one study is desirable, it requires extensive clinical data collection with an extended follow-up period in a large cohort, such as that available in the MD STAR*net*. Further, in previous related studies, DMD patients were followed mostly to the mid- or late-teenage years [7,9,11,12,21], whereas the MD STAR*net* followed some cases to their late-twenties.

Even with this data resource, our study has several limitations. First, our data were collected from medical record abstraction, which does not involve assessment at fixed intervals for all cases. Thus, not all cases were evaluated for each clinical outcome using formal clinical testing, nor were those tested evaluated at regular, predefined intervals. As a result, detection bias may have been introduced. For example, the cases who started corticosteroids earlier may have had more frequent clinician contact than those who started later; therefore, their cardiomyopathy possibly could be diagnosed at an earlier age. Second, we did not separate drug type, dosage regimen, or dosing interval for the early and late childhood treatment groups, which may have impacted our findings regarding side-effects [44] because it further reduced sample size in the treated group due to lack of data. Overall, of the 2750 corticosteroid treatment episodes documented for the cases in MD STAR*net*, by drug type, 66% were treated with prednisone, 29% with deflazacort, and 5% were missing. By dosing interval, 74% had the treatment daily, 16% every other day, 7% two days/week, and 3% other intervals. Since the MD STAR*net* abstractors only recorded the total dose (mg), not the dose per body weight (e.g., mg/kg), dosage information were not provided. Third, our cases were limited to those with age at onset of first signs or symptoms before age 6 years to exclude Becker muscular dystrophy cases. Sometimes, age at loss of ambulation is used to

differentiate between Becker and Duchenne cases, but the age of loss of ambulation can be modified by treatment and management. A standard age cutoff for this differentiation is not widely accepted, especially when individuals receive corticosteroids. Despite use of age at first onset of signs or symptoms to exclude Becker-like dystrophinopathy, our data may have some individuals with the Becker phenotype in the untreated and late groups, because there were individuals still ambulating after age 15 years. Fourth, as the data came from medical record abstraction, the method of right-censoring age (i.e., age at last available clinical test or age at last clinic visit) may produce systemic bias. The former censoring scheme excludes cases that did not have documented clinical evaluation of the outcome during the study. The absence of a clinical test may or may not indicate normal function with regard to the clinical outcomes examined due to young age, at which a clinical test may not be warranted, clinical symptoms that are not strong enough to prompt a clinical test, or the absence of clinical symptoms upon evaluation by the neuromuscular physician. Alternatively, when censoring at the last clinic visit, we cannot assume normal function for the clinical outcomes examined at this visit without a clinical test, and perhaps the last clinic visit occurred in a specialty clinic in which only a single outcome was assessed. Overall, our results were similar for both right censoring approaches used. Fifth, although our data collection was longitudinal, the median follow-up years might not have been long enough; median follow-up age in years [range] were 13 [1–29], 11 [3–28], 15 [6–31] for treatment naïve, early, and late childhood treatment groups, respectively. It is possible that we did not precisely capture the clinical patterns of cases at their later ages. Sixth, the small sample size in the early childhood treatment group ($n \leq 60$) relative to the other groups provides low statistical power for the detection of any statistical difference of clinical function between this and the other groups. Seventh, it is possible that we have underestimated the age at loss of ambulation since ambulation can be lost abruptly after a fall and fracture that can end walking much earlier. Lastly, our study lacked genetic test data for some cases; it has been suggested that genetic markers of disease progress such as Osteopontin or LTBP4 genotype may affect the progression of some of the clinical outcomes examined [45,46].

In conclusion, we found evidence that DMD cases in the MD STAR*net* who initiated corticosteroid treatment during early childhood were likely to have a higher risk of developing earlier onset cardiomyopathy, suffering a fracture, and decreased respiratory function, compared to cases who initiated treatment in late childhood or were treatment naïve. Although there is increasing interest in the effects of early childhood treatment with corticosteroids on clinical outcomes [47] and apparently more clinicians are prescribing corticosteroid treatment earlier, the available data to comprehensively evaluate such effects in extended follow-up periods are scant. Because corticosteroids remain a treatment of choice for DMD, continued, careful assessments of the timing of initiating of this treatment are needed. Our study can be a valuable reference for these future studies.

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References

1. Hoffman EP, Brown RH Jr, Kunkel LM. Dystrophin: the protein product of the Duchenne muscular dystrophy locus. Cell. 1987; 51(6):919–28. [PubMed: 3319190]
2. Bushby K, Muntoni F, Urtizberea A, Hughes R, Griggs R. Report on the 124th ENMC International Workshop. Treatment of Duchenne muscular dystrophy; defining the gold standards of management in the use of corticosteroids. 2–4 April 2004, Naarden, The Netherlands. Neuromuscul Disord. 2004; 14(8–9):526–34. [PubMed: 15336694]
3. Romitti PA, Zhu Y, Puzhankara S, James KA, Nabukera SK, Zamba GK, et al. Prevalence of Duchenne and Becker muscular dystrophies in the United States. Pediatrics. 2015; 135(3):513–21. [PubMed: 25687144]
4. Ishikawa Y, Miura T, Ishikawa Y, Aoyagi T, Ogata H, Hamada S, et al. Duchenne muscular dystrophy: survival by cardio-respiratory interventions. Neuromuscul Disord. 2011; 21(1):47–51. [PubMed: 21144751]
5. Eagle M, Baudouin SV, Chandler C, Giddings DR, Bullock R, Bushby K. Survival in Duchenne muscular dystrophy: improvements in life expectancy since 1967 and the impact of home nocturnal ventilation. Neuromuscul Disord. 2002; 12(10):926–9. [PubMed: 12467747]
6. Balaban B, Matthews DJ, Clayton GH, Carry T. Corticosteroid treatment and functional improvement in Duchenne muscular dystrophy: long-term effect. Am J Phys Med Rehabil. 2005; 84(11):843–50. [PubMed: 16244521]
7. Houde S, Filiatrault M, Fournier A, Dubé J, D'Arcy S, Bérubé D, et al. Deflazacort use in Duchenne muscular dystrophy: an 8-year follow-up. Pediatr Neurol. 2008; 38(3):200–6. [PubMed: 18279756]
8. King WM, Ruttencutter R, Nagaraja HN, Matkovic V, Landoll J, Hoyle C, et al. Orthopedic outcomes of long-term daily corticosteroid treatment in Duchenne muscular dystrophy. Neurology. 2007; 68(19):1607–13. [PubMed: 17485648]
9. Merlini L, Gennari M, Malaspina E, Cecconi I, Armaroli A, Gnudi S, et al. Early corticosteroid treatment in 4 Duchenne muscular dystrophy patients: 14-year follow-up. Muscle Nerve. 2012; 45(6):796–802. [PubMed: 22581531]
10. 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(4): 249–55. [PubMed: 16545568]
11. 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(4):386–91. [PubMed: 8170484]
12. DeSilva S, Drachman DB, Mellits D, Kuncl RW. Prednisone treatment in Duchenne muscular dystrophy. Long-term benefit. Arch Neurol. 1987; 44(8):818–22. [PubMed: 3632394]
13. Henricson EK, Abresch RT, Cnaan A, Hu F, Duong T, Arrieta A, et al. The cooperative international neuromuscular research group Duchenne natural history study: glucocorticoid treatment preserves clinically meaningful functional milestones and reduces rate of disease progression as measured by manual muscle testing and other commonly used clinical trial outcome measures. Muscle Nerve. 2013; 48(1):55–67. [PubMed: 23649481]
14. Barber BJ, Andrews JG, Lu Z, West NA, Meaney FJ, Price ET, et al. Oral corticosteroids and onset of cardiomyopathy in Duchenne muscular dystrophy. J Pediatr. 2013; 163(4):1080–4. [PubMed: 23866715]
15. Mavrogeni S, Papavasiliou A, Douskou M, Kolovou G, Papadopoulou E, Cokkinos DV. Effect of deflazacort on cardiac and sternocleidomastoid muscles in Duchenne muscular dystrophy: a magnetic resonance imaging study. Eur J Paediatr Neurol. 2009; 13(1):34–40. [PubMed: 18406648]
16. Silversides CK, Webb GD, Harris VA, Biggar DW. Effects of deflazacort on left ventricular function in patients with Duchenne muscular dystrophy. Am J Cardiol. 2003; 91(6):769–72. [PubMed: 12633823]

17. Markham LW, Spicer RL, Khoury PR, Wong BL, Mathews KD, Cripe LH. Steroid therapy and cardiac function in Duchenne muscular dystrophy. Pediatr Cardiol. 2005; 26(6):768–71. [PubMed: 15990951]

18. Finsterer J, Stöllberger C. Corticosteroid treatment retards development of ventricular dysfunction in Duchenne muscular dystrophy. Neuromuscul Disord. 2009; 19(1):74. author reply 75. [PubMed: 19070488]

19. Biggar WD, Gingras M, Fehlings DL, Harris VA, Steele CA. Deflazacort treatment of Duchenne muscular dystrophy. J Pediatr. 2001; 138:45–50. [PubMed: 11148511]

20. Griggs RC, Moxley RT 3rd, Mendell JR, Fenichel GM, Brooke MH, Pestronk A, 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(4):383–8. [PubMed: 2012511]

21. Fenichel GM, Florence JM, Pestronk A, Mendell JR, Moxley RT 3rd, Griggs RC, et al. Long-term benefit from prednisone therapy in Duchenne muscular dystrophy. Neurology. 1991; 41(12):1874–7. [PubMed: 1745340]

22. Mendell JR, Moxley RT, Griggs RC, Brooke MH, Fenichel GM, Miller JP, et al. Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. N Engl J Med. 1989; 320(24):1592–7. [PubMed: 2657428]

23. Duboc D, Meune C, Lerebours G, Devaux JY, Vaksmann G, Becane HM. Effect of perindopril on the onset and progression of left ventricular dysfunction in Duchenne muscular dystrophy. J Am Coll Cardiol. 2005; 45:855–7. [PubMed: 15766818]

24. Duboc D, Meune C, Pierre B, Wahbi K, Eymard B, Toutain A, et al. Perindopril preventive treatment on mortality in Duchenne muscular dystrophy: 10 years' follow-up. Am Heart J. 2007; 154(3):596–602. [PubMed: 17719312]

25. Manzur AY, Kuntzer T, Pike M, Swan A. Glucocorticoid corticosteroids for Duchenne muscular dystrophy. Cochrane Database Syst Rev. 2008; (1):CD003725. [PubMed: 18254031]

26. Bushby K, Finkel R, Birnkrant DJ, Case LE, Clemens PR, Cripe L, DMD Care Considerations Working Group. et al. Diagnosis and management of Duchenne muscular dystrophy, part 1: diagnosis, and pharmacological and psychosocial management. Lancet Neurol. 2010; 9(1):77–93. [PubMed: 19945913]

27. Shah D. Are corticosteroids effective in Duchenne muscular dystrophy. Indian Pediatr. 2008; 45(5): 401–2. [PubMed: 18515930]

28. Gloss D, Moxley RT 3rd, Ashwal S, Oskoui M. Practice guideline update summary: corticosteroid treatment of Duchenne muscular dystrophy: report of the Guideline Development Subcommittee of the American Academy of Neurology. Neurology. 2016; 86(5):465–72. [PubMed: 26833937]

29. Matthews E, Brassington R, Kuntzer T, Jichi F, Manzur AY. Corticosteroids for the treatment of Duchenne muscular dystrophy. Cochrane Database Syst Rev. 2016; (5):CD003725. [PubMed: 27149418]

30. Carter GT, McDonald CM. Preserving function in Duchenne dystrophy with long-term pulse prednisone therapy. Am J Phys Med Rehabil. 2000; 79(5):455–8. [PubMed: 10994887]

31. Dubowitz V, Kinali M, Main M, Mercuri E, Muntoni F. Remission of clinical signs in early Duchenne muscular dystrophy on intermittent low-dosage prednisolone therapy. Eur J Paediatr Neurol. 2002; 6(3):153–9. [PubMed: 12363102]

32. Kinali M, Mercuri E, Main M, Muntoni F, Dubowitz V. An effective, low-dosage, intermittent schedule of prednisolone in the long-term treatment of early cases of Duchenne dystrophy. Neuromuscul Disord. 2002; 12(Suppl. 1):S169–74. [PubMed: 12206813]

33. Mathews KD, Cunniff C, Kantamneni JR, Ciafaloni E, Miller T, Matthews D, et al. Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet): case definition in surveillance for childhood-onset Duchenne/Becker muscular dystrophy. J Child Neurol. 2010; 25(9):1098–102. [PubMed: 20817884]

34. Miller LA, Romitti PA, Cunniff C, Druschel C, Mathews KD, Meaney FJ, et al. The muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet): surveillance methodology. Birth Defects Res A Clin Mol Teratol. 2006; 76(11):793–7. [PubMed: 17036307]

35. Lipshultz SE, Sleeper LA, Towbin JA, Lowe AM, Orav EJ, Cox GF, et al. The incidence of pediatric cardiomyopathy in two regions of the United States. N Engl J Med. 2003; 348(17):1647–55. [PubMed: 12711739]
36. Jefferies JL, Eidem BW, Belmont JW, Craigen WJ, Ware SM, Fernbach SD, et al. Genetic predictors and remodeling of dilated cardiomyopathy in muscular dystrophy. Circulation. 2005; 112(18):2799–804. [PubMed: 16246949]
37. Nagai T. Prognostic evaluation of congestive heart failure in patients with Duchenne muscular dystrophy – retrospective study using non-invasive cardiac function tests. Jpn Circ J. 1989; 53(5): 406–15. [PubMed: 2769928]
38. Viollet L, Thrush PT, Flanigan KM, Mendell JR, Allen HD. Effects of angiotensin-converting enzyme inhibitors and/or beta blockers on the cardiomyopathy in Duchenne muscular dystrophy. Am J Cardiol. 2012; 110(1):98–102. [PubMed: 22463839]
39. Wei LJ, Lin DY, Weissfeld L. Regression analysis of multivariate incomplete failure time data by using the marginal distributions. JASA. 1989; 84:1065–73.
40. American Heart Association, Inc. Cardiac medications. 2012. Available from: https://www.heart.org/idc/groups/heart-public/@wcm/@hcm/documents/downloadable/ucm_304568.pdf
41. Ferlini A, Sewry C, Melis MA, Mateddu A, Muntoni F. X-linked dilated cardiomyopathy and the dystrophin gene. Neuromuscul Disord. 1999; 9(5):339–46. [PubMed: 10407857]
42. Townsend D, Yasuda S, Chamberlain J, Metzger JM. Cardiac consequences to skeletal muscle-centric therapeutics for Duchenne muscular dystrophy. Trends Cardiovasc Med. 2009; 19(2):50–5. [PubMed: 19577712]
43. Alman BA, Raza SN, Biggar WD. Steroid treatment and the development of scoliosis in males with Duchenne muscular dystrophy. J Bone Joint Surg Am. 2004; 86-A(3):519–24. [PubMed: 14996877]
44. Biggar WD, Politano L, Harris VA, Passamano L, Vajsar J, Alman B, et al. Deflazacort in Duchenne muscular dystrophy: a comparison of two different protocols. Neuromuscul Disord. 2004; 14(8–9):476–82. [PubMed: 15336688]
45. Pegoraro E, Hoffman EP, Piva L, Gavassini BF, Cagnin S, Ermani M, et al. SPP1 genotype is a determinant of disease severity in Duchenne muscular dystrophy. Neurology. 2011; 76(3):219–26. [PubMed: 21178099]
46. Flanigan KM, Ceco E, Lamar KM, Kaminoh Y, Dunn DM, Mendell JR, et al. LTBP4 genotype predicts age of ambulatory loss in Duchenne muscular dystrophy. Ann Neurol. 2013; 73(4):481–8. [PubMed: 23440719]
47. Muscular Dystrophy Association. MDA Funds Study of Prednisone in Very Young Boys with DMD. 2013. Available from: http://quest.mda.org/news/mda-funds-study-prednisone-very-young-boys-dmd. [Accessed 11November 2016]

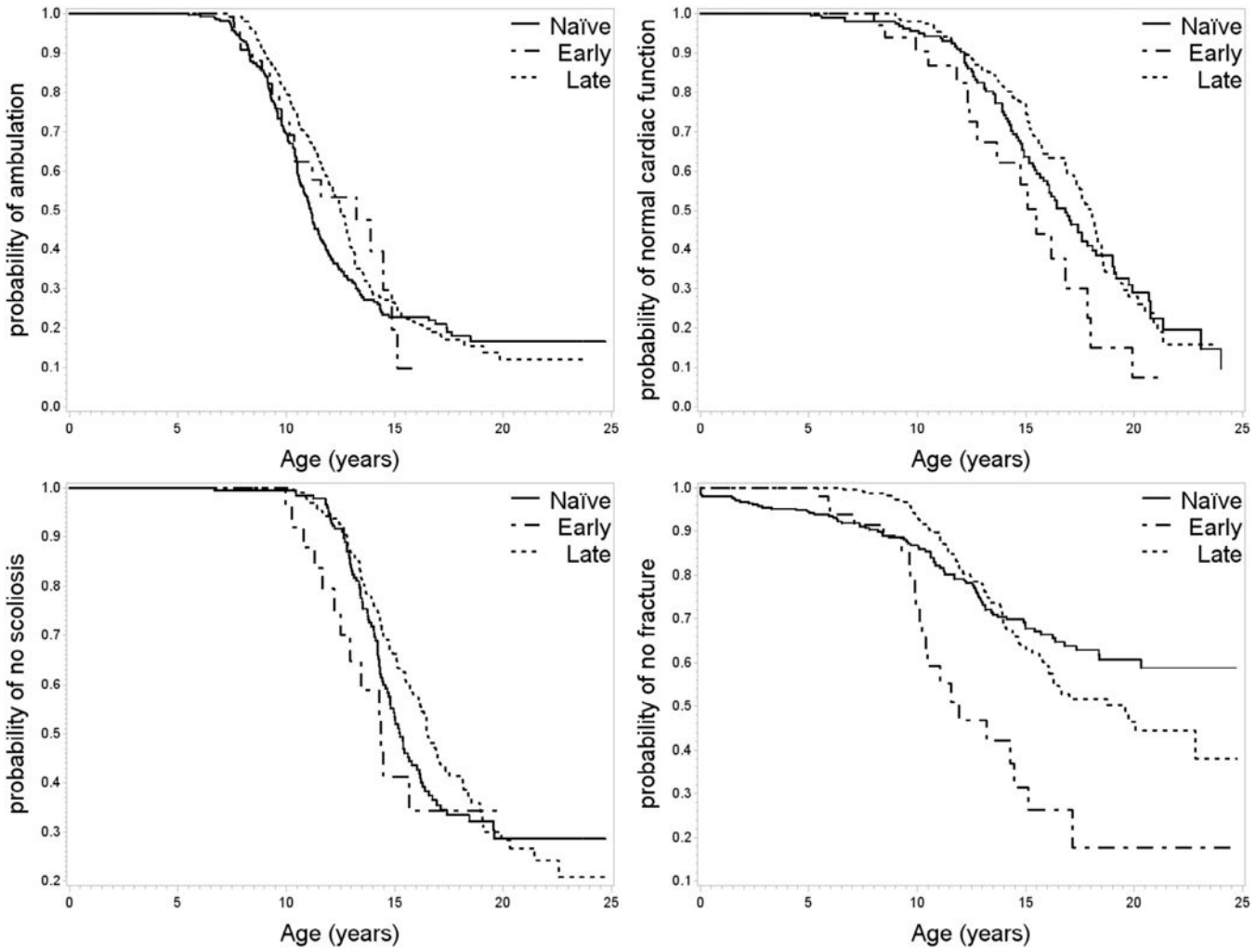

Fig. 1.

Kaplan–Meier curve for loss of ambulation, onset of cardiomyopathy, scoliosis, and fracture by timing of corticosteroid treatment initiation. The Y-axis value represents the probability of ambulation, and probability free from onset of cardiomyopathy, scoliosis, or fracture accordingly (Muscular Dystrophy Surveillance Tracking, and Research Network, 1982–2011).

Table 1

Kaplan–Meier estimates of median (95% CI) age (years) of clinical outcomes by timing of corticosteroid treatment initiation (Muscular Dystrophy Surveillance Tracking, and Research Network, 1982–2011).

	Total	Naïve			Early treated			Late treated		
	N	N	Event	Median age	N	Event	Median age	N	Event	Median age
For those with available clinical test record, right censoring at their last record										
Loss of ambulation	632	325	172	11.1 (10.7, 11.6)	59	20	13.2 (10.4, 14.9)	248	161	12.5 (12.0, 12.8)
Cardiomyopathy onset	481	216	88	16.8 (15.7, 17.8)	47	18	15.5 (12.8, 17.8)	218	85	18.0 (16.9, 18.5)
First scoliosis	553	279	98	15.2 (14.7, 16.2)	43	13	14.4 (12.5, 15.6)	231	94	14.2 (13.4, 14.7)
For all, right censoring at last clinic visit										
Loss of ambulation	654	342	172	11.2 (10.8, 11.6)	60	20	13.2 (10.4, 14.9)	252	161	12.6 (12.1, 12.9)
Cardiomyopathy onset	660	342	88	19.0 (17.1, 20.8)	59	18	16.2 (13.7, 18.0)	259	85	18.7 (18.0, 19.8)
First scoliosis	666	342	93	16.2 (15.2, 19.6)	60	13	14.5 (13.0, –)	264	94	17.3 (16.5, 18.9)
First fracture *	625	341	82	Not available †	55	22	11.5 (10.2, 15.1)	229	81	19.6 (16.1, –)

*Because a fracture was recorded when it happened, cases without fractures were right censored only at the age of their last clinic visit.

†Because probability of no fracture was >0.5 by age 25, the age that the probability of no fracture reaches 0.5 could not be calculated.

Table 2

Hazard ratios (HR) for loss of ambulation, cardiomyopathy onset, first scoliosis, and first fracture for early vs naïve, early vs late, naïve vs late treatment groups (Muscular Dystrophy Surveillance Tracking, and Research Network, 1982–2011).

	Early vs naïve		Early vs late		Naïve vs late	
	HR (95% CI)	**P**	**HR (95% CI)**	**P**	**HR (95% CI)**	**P**
For those with available clinical test record, right censoring at their last record						
Loss of ambulation [*]	0.8 (0.5, 1.3)	0.46	1.0 (0.6, 1.6)	0.91	1.2 (1.0, 1.5)	0.06
Cardiomyopathy onset [†]	**1.9 (1.1, 3.2)**	**0.02**	**2.0 (1.2, 3.4)**	**0.01**	1.1 (0.8, 1.5)	0.67
First scoliosis [*]	1.3 (0.9, 1.6)	0.35	1.5 (0.9, 2.7)	0.15	1.2 (0.9, 1.6)	0.29
For all, right censoring at last clinic visit						
Loss of ambulation [*]	0.9 (0.5, 1.3)	0.48	1.0 (0.7, 1.7)	0.88	1.2 (1.0, 1.5)	0.06
Cardiomyopathy onset [†]	**2.1 (1.2, 3.5)**	**<0.01**	**2.1 (1.2, 3.5)**	**0.01**	1.0 (0.7, 1.3)	0.95
First scoliosis [*]	1.6 (0.9, 2.8)	0.14	1.7 (0.9, 3.0)	0.08	1.1 (0.8, 1.4)	0.56
First fracture [*,‡]	**2.6 (1.6, 4.2)**	**<0.01**	**2.3 (1.4, 3.7)**	**<0.01**	0.9 (0.6, 1.2)	0.40

Bold text indicates a statistically significant difference with Bonferroni-corrected $P \leq 0.02$.

[*] Adjusted for age at onset (of first signs and symptoms).

[†] Adjusted for age at onset and use of cardiac medications.

[‡] Because a fracture was recorded when it happened, cases without fractures were right censored only at the age of their last clinic visit.

Table 3

Expected difference of forced vital capacity (FVC, L) from linear regression* for early vs naïve, early vs late, naïve vs late treatment groups (Muscular Dystrophy Surveillance Tracking, and Research Network, 1982–2011).

	Early vs naïve		Early vs late		Naïve vs late	
	Difference (SE)	**P**	**Difference (SE)**	**P**	**Difference (SE)**	**P**
FVC, L (SE)	−0.18 (0.12)	0.15	**−0.39 (0.12)**	**<0.01**	−0.21 (0.10)	0.04

Bold text indicates a statistically significant difference with Bonferroni-corrected $P \leq 0.02$.

*Adjusted for age at onset of first signs and symptoms, and age at pulmonary function test.