Oral Corticosteroids and Onset of Cardiomyopathy in Duchenne Muscular Dystrophy

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Objective To estimate the age when cardiomyopathy develops in boys with Duchenne muscular dystrophy (DMD) and to analyze the effect of corticosteroid treatment on the age of cardiomyopathy onset.

Study design We identified a population-based sample of 462 boys with DMD, born between 1982 and 2005, in 5 surveillance sites in the US. Echocardiographic and corticosteroid treatment data were collected. Cardiomyopathy was defined by a reduced fractional shortening (<28%) or ejection fraction (<55%). The age of cardiomyopathy onset was determined. Survival analysis was performed to determine the effects of corticosteroid treatment on cardiomyopathy onset.

Results The mean (SD) age of cardiomyopathy onset was 14.3 (4.2) years for the entire population and 15.2 (3.4) years in corticosteroid-treated vs 13.1 (4.8) in non-treated boys. Survival analysis described a significant delay of cardiomyopathy onset for boys treated with corticosteroids (P < .02). By 14.3 years of age, 63% of non-treated boys had developed cardiomyopathy vs only 36% of those treated. Among boys treated with corticosteroids, there is a significant positive effect of duration of corticosteroid treatment on cardiomyopathy onset (P < .0001). For every year of corticosteroid treatment, the probability of developing cardiomyopathy decreased by 4%.

Conclusions Oral corticosteroid treatment was associated with delayed cardiomyopathy onset. The duration of corticosteroid treatment also correlated positively with delayed cardiomyopathy onset. Our analysis suggests that a boy with DMD treated for 5 years with corticosteroids might experience a 20% decrease in the likelihood of developing cardiomyopathy compared with untreated boys. (J Pediatr 2013;163:1080-4).

In 1883, Ross described cardiac abnormalities found at autopsy in a boy with characteristic features of Duchenne muscular dystrophy (DMD).1 Since that time, advances in clinical management, particularly use of pulmonary interventions, have prolonged the life expectancy of boys with DMD.2 With prolonged survival, heart failure has now become a leading cause of death.3 The cardiac disease of DMD is typically a dilated cardiomyopathy primarily involving the left ventricle (LV) and characterized by myocyte fibrosis, thinning of LV walls, and decreased contractility.4 The onset of cardiomyopathy is often insidious, and the age when it occurs is variable, but typically by age 18 all boys with DMD have evidence of cardiac dysfunction.5

The diminished skeletal muscle strength and reduced physical activity of boys with DMD frequently mask the clinical symptoms of heart failure until advanced stages of LV dysfunction are reached. Regular cardiac screening evaluations have therefore been recommended for early identification and treatment of cardiomyopathy.5,6 Oral corticosteroids are now routinely prescribed for boys with DMD to preserve skeletal muscle strength, reduce the risk of scoliosis, and stabilize pulmonary function.7-10 The cardiac effects of corticosteroid treatment are not well characterized, although previous, smaller investigations have identified possible benefits.11-13 On the other hand, evidence from human and mouse studies suggest that preserved skeletal muscle function may place undue stress on a vulnerable myocardium, leading to earlier onset of cardiomyopathy.14,15 Guidelines for cardiac health in DMD call for further research into the effects of corticosteroids.3

The purpose of this investigation was to describe the time course of cardiomyopathy onset in a population-based cohort of boys with DMD, including both those treated with corticosteroids and those not treated, and to determine if oral corticosteroid treatment influences cardiomyopathy onset in boys with DMD.

ACE Angiotensin-converting enzyme
DMD Duchenne muscular dystrophy
EF Ejection fraction
FS Fractional shortening
LV Left ventricle
MD STARnet Muscular Dystrophy Surveillance, Tracking, and Research Network

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Methods

The Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet) is a population-based surveillance program that collects standardized information on people with Duchenne and Becker muscular dystrophy from Arizona, Colorado, Georgia, Iowa, and western New York State. Data are collected from inpatient and outpatient records from multiple medical sources. The case definition for DMD is based on clinical phenotype and supportive dystrophin gene mutation and/or muscle biopsy results. A full description of the MD STARnet surveillance methodology has been published previously. Each study site maintains Institutional Review Board approval for this research. MD STARnet patients in this analysis consisted of 797 males who were born between January 1, 1982 and December 31, 2005, for whom there were case records before October 1, 2010. Among these 797 individuals, we excluded 200 patients because their cardiac function could not be determined through echocardiographic records. We also excluded an additional 128 individuals whose steroid treatment could not be classified, and 7 individuals who continued ambulation past 17 years of age and whose phenotype was therefore most consistent with Becker muscular dystrophy. Thus, a total of 462 patients were included in the regression sample (Figure 1; available at www.jpeds.com).

Age of ceased ambulation was defined as the age at which the individual was first reported as either having ceased ambulation or having documentation of being a fulltime wheelchair user without any evidence of ambulation occurring after that age.

An echocardiogram was considered diagnostic of cardiomyopathy if it demonstrated a fractional shortening (FS) of <28%, or if FS information was not available, by an ejection fraction (EF) <55%. If neither FS nor EF were reported, then FS was calculated using M-Mode data of LV end-diastolic and end systolic dimensions. These standard measures of function have been shown in other studies of patients with DMD to be robust markers of systolic function and are used clinically for diagnosis of cardiomyopathy. An echocardiogram was considered diagnostic of cardiomyopathy if it demonstrated a fractional shortening (FS) of <28%, or if FS information was not available, by an ejection fraction (EF) <55%. If neither FS nor EF were reported, then FS was calculated using M-Mode data of LV end-diastolic and end systolic dimensions. These standard measures of function have been shown in other studies of patients with DMD to be robust markers of systolic function and are used clinically for diagnosis of cardiomyopathy. An echocardiogram was considered diagnostic of cardiomyopathy if it demonstrated a fractional shortening (FS) of <28%, or if FS information was not available, by an ejection fraction (EF) <55%. If neither FS nor EF were reported, then FS was calculated using M-Mode data of LV end-diastolic and end systolic dimensions. These standard measures of function have been shown in other studies of patients with DMD to be robust markers of systolic function and are used clinically for diagnosis of cardiomyopathy. An echocardiogram was considered diagnostic of cardiomyopathy if it demonstrated a fractional shortening (FS) of <28%, or if FS information was not available, by an ejection fraction (EF) <55%. If neither FS nor EF were reported, then FS was calculated using M-Mode data of LV end-diastolic and end systolic dimensions. These standard measures of function have been shown in other studies of patients with DMD to be robust markers of systolic function and are used clinically for diagnosis of cardiomyopathy. An echocardiogram was considered diagnostic of cardiomyopathy if it demonstrated a fractional shortening (FS) of <28%, or if FS information was not available, by an ejection fraction (EF) <55%. If neither FS nor EF were reported, then FS was calculated using M-Mode data of LV end-diastolic and end systolic dimensions. These standard measures of function have been shown in other studies of patients with DMD to be robust markers of systolic function and are used clinically for diagnosis of cardiomyopathy.

The two echocardiographic variables used for analysis were the age at the time of the most recently documented normal echocardiogram and, if applicable, age at the time of the first documented abnormal echocardiogram. For those with a documented abnormal echocardiogram, the last normal echocardiogram was defined as the last exam immediately preceding the abnormal value, and for those without an abnormal echocardiogram, it was the last documented exam in the record.

An individual with cardiomyopathy onset was considered to be corticosteroid-treated if medical records documented that he was taking prednisone, prednisolone, or deflazacort for a minimum of 1 month any time prior to cardiomyopathy diagnosis. An individual without cardiomyopathy onset was considered to be corticosteroid-treated if medical records documented that he was taking prednisone, prednis-

Statistical Analyses

Data analysis was performed utilizing R 2.14.0 software (http://www.r-project.org). An accelerated failure time survival regression model with interval censoring was used to analyze the effects of our variables of interest. Interval censoring is used in order to better estimate an event (ie, onset of cardiomyopathy) which has occurred at an unknown point within a time interval; namely, the interval between the age of last normal echocardiogram and the age of first abnormal echocardiogram. This is especially important when analyzing medical histories in which large or variable gaps in service may have occurred. This approach also allows us to analyze patients who have not yet experienced cardiomyopathy onset and those who have no record of a previous normal echocardiogram. Correlations were used to determine relationships between the variables of interest; χ² tests were used to compare the regression sample to the MD STARnet population.

Table I illustrates the composition of cases from the analytical dataset and compares it with the entire MD STARnet population. No significant differences were found between the sample and the MD STARnet population for race/ethnicity or patient distribution per surveillance site (state).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Analytical Dataset</th>
<th>MD STARnet Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of ceased ambulation</td>
<td>13.1 (4.8) years</td>
<td>7.4 (2.5) years</td>
</tr>
<tr>
<td>Corticosteroid treatment</td>
<td>58.7%</td>
<td>69.4%</td>
</tr>
<tr>
<td>Mean corticosteroid treatment duration</td>
<td>7.4 (2.5) years</td>
<td>6.1 (3.4) years</td>
</tr>
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</table>

Of the 462 patients included in the analytical dataset, 291 were corticosteroid-treated with a mean treatment start age of 7.4 (2.5) years and a mean corticosteroid treatment duration of 4.1 (3.4) years. The percentage of boys receiving corticosteroids among the MD STARnet sites ranged from 56.7% to 69.4% and was not significantly different (P = .23). Within the dataset, 292 individuals had ceased ambulation with a mean cessation age of 10.8 (2.1) years. There was a positive correlation (r = 0.3, P < .01) between age of ceased ambulation and duration of corticosteroid treatment. For those individuals in the cohort who developed cardiomyopathy onset (n = 202), the mean age of cardiomyopathy onset diagnosis was 14.3 (4.2) years with a normal distribution as shown in Figure 2. The mean age of cardiomyopathy onset in corticosteroid-treated individuals was 15.2 (3.4) years, and the mean age of cardiomyopathy onset in non-treated individuals was 13.1 (4.8) years.

There was significant multicollinearity among the 4 possible predictor variables: corticosteroid treatment status,
corticosteroid start age, corticosteroid treatment duration, and age of ceased ambulation. This was addressed by including only 1 predictor variable, corticosteroid treatment duration, in the survival regression model. Steroid duration was selected over steroid start age because of the complexity of estimating a model with interval censoring and time-dependent predictors.

In Figure 3, a Kaplan–Meier survival curve illustrates the cardioprotective effects of corticosteroid treatment in DMD, with a significantly delayed cardiomyopathy onset in the treated (n = 291) vs non-treated group (n = 171) (P = 0.02, \( \chi^2 = 5.27 \)). A summary of the results of the accelerated failure time survival regression model is shown in Table II. Among boys treated with corticosteroids, there is a significant positive effect of duration of corticosteroid treatment on cardiomyopathy onset (P < .0001). Additionally, the regression analysis demonstrated that for every year of corticosteroid treatment, cardiomyopathy onset was delayed by 4%.

## Discussion

Progressive cardiac dysfunction is a hallmark of DMD, although the time course for cardiomyopathy is not well characterized.\(^3\),\(^21\) In our population-based cohort of 202 boys with DMD who developed cardiomyopathy, we found the mean age of cardiomyopathy onset was 14.3 years. This is comparable with previous studies documenting cardiomyopathy onset in patients with DMD.\(^5\),\(^18\),\(^22\) In a single institution study of 62 boys with DMD, Jefferies et al investigated cardiomyopathy as defined by reduced systolic function or LV dilation and found that 31 of them developed cardiomyopathy at a mean age (SD) of 15.4 (2.8) years.\(^18\) Although the endpoint of these investigations is cardiomyopathy onset, it is important to recognize that the transition from normal function to cardiomyopathy onset represents a continuum and that emerging cardiac imaging techniques, such as assessments of diastolic function, strain, and myocardial scarring, are likely to change the ways in which cardiomyopathy onset will be defined.\(^23\),\(^24\)

In 2004, the European Neuro-Muscular Centre International Workshop concluded that corticosteroids are indicated in the management in DMD, based on the results of multiple studies reporting preserved skeletal muscle strength and prolonged ambulation, improved respiratory function, and decreased need for scoliosis surgery.\(^7\) At that time there were limited reports on the cardiac consequences of corticosteroid treatment, but there was some suggestion of benefit.\(^25\)

In 2005, the American Academy of Pediatrics published cardiovascular health supervision guidelines for DMD patients and called for more studies to evaluate the cardiac effects.
effects of corticosteroids in boys with DMD. In that same year, Markham et al reported on LV function in 48 boys with DMD who were treated with corticosteroids (mean age at initiation = 6.7 years and mean length of treatment = 3 years) and compared them with 63 untreated boys. Those who received corticosteroid treatment were significantly less likely to develop LV dysfunction than those who were untreated. The cardiac benefits did not differ based on the type of corticosteroid prescribed and appeared to persist after discontinuation of corticosteroid treatment for those who were treated for longer than 6 months. A follow-up study by the same authors in 2008 analyzed LV function in 14 boys treated with corticosteroids and 23 who were untreated and again noted a beneficial effect. A more recent investigation of 63 corticosteroid-treated and 23 non-treated individuals found a lower rate of new-onset cardiomyopathy and a significant reduction in all-cause mortality for those who were corticosteroid treated. Despite these observations, concerns persist regarding the potential cardiac risks of corticosteroids, including obesity, systemic hypertension, LV hypertrophy, and decreased cardiac function. The cardioprotective mechanisms of corticosteroids are speculative but may include cell membrane stabilization, reduced myocardial inflammation and fibrosis, or secondary cardiac effects that result from improved skeletal muscle function and delayed progression of scoliosis and respiratory insufficiency. More advanced cardiac imaging studies on corticosteroid-treated boys with DMD may provide additional insight into the mechanisms. The optimal cardiac treatment regimen for boys with DMD remains to be determined. Angiotensin-converting enzyme (ACE) inhibitors have also shown promise in delaying cardiomyopathy onset, and it is possible that a combination of ACE inhibition with corticosteroid treatment may add increased benefit. Prophylactic treatment with ACE inhibitors was reported by Duboc et al in 2005, so treatment with ACE inhibitors prior to cardiomyopathy onset was not common during the timeframe of our analysis. Although we were unable to analyze the effects of all cardiac medications in our analysis systematically, we did observe that fewer than 8% of patients had evidence of ACE inhibitor treatment prior to cardiomyopathy onset. Removal of this subset of patients from our survival analysis did not alter our findings, affirming that the observed benefit of corticosteroid treatment on cardiomyopathy onset was not confounded by ACE treatment.

Concern has been raised regarding an increased risk of cardiomyopathy in subjects with preserved skeletal muscle function. Jefferies et al reported earlier cardiomyopathy onset in patients with Becker muscular dystrophy and prolonged ambulation when compared with boys with DMD. Studies in dystrophin deficient mice have also shown that expression of some dystrophin in skeletal muscle increases exercise capacity but results in cardiac damage. The more active mice have significantly more myocardial necrosis and ventricular dilation than the less active mice. These findings point to a potentially negative cardiac consequence of corticosteroid treatment, which prolongs ambulation and skeletal muscle strength but may cause increased stress on the myocardium and accelerate cardiomyopathy onset. These findings also have implications for gene therapies designed to restore dystrophin function and improve skeletal muscle strength but which may also subject cardiac muscle to increased stress and damage. In the current investigation, however, we found that corticosteroids exerted a cardioprotective effect. There was also a strong positive correlation between duration of corticosteroid treatment and the age of ceased ambulation (r = 0.3, P < .01), which indicates that those individuals who ceased ambulation at older ages had later cardiomyopathy onset. This suggests that increased skeletal muscle use in the patient with DMD is either: (1) not associated with an acceleration in cardiomyopathy onset; or (2) that the potential negative cardiac consequences of increased skeletal muscle use are overcome by direct beneficial cardiac effects of corticosteroids.

The strengths of the MD STARnet cohort are important to consider. This is the largest sample of boys with DMD that has been examined for the effects of corticosteroid treatment on cardiac function. This cohort is population-based, which minimizes the referral bias of previous reports from specialty clinics or treatment centers. MD STARnet data collection is standardized and is gathered by a common protocol used at all surveillance sites. The limitations of this study are also important to recognize. Because MD STARnet is record-based, data are not always available for all variables of interest on each individual, including other potential echocardiographic measures that could be used to diagnose cardiomyopathy. Echocardiograms were performed by multiple sonographers using various echocardiography systems and were interpreted by multiple cardiologists at different centers. Although this may have introduced inconsistencies in the variables analyzed, the standard m-mode measures of cardiac systolic function (FS and EF) have been shown to be highly reproducible. Additionally, morbidities associated with steroid use such as hypertension, obesity, osteoporosis, and diabetes could not be assessed reliably from the available data. It is important to recognize, however, that despite any negative consequences of these morbidities, we still observed an overall beneficial effect of corticosteroid treatment on cardiomyopathy onset. In addition, genetic factors could not be reliably assessed because mutation information was not available for all patients. Additional studies are needed to determine the optimal corticosteroid dose, duration of treatment, and the potential

| Parameter estimates of accelerated failure time survival regression model |
|----------------------|--------|-------|------|------|---|
| Estimate       | SE     | Z     | CI   | P value |
| Steroid use duration (year) | 0.04   | 0.007 | 5.2  | 0.026, 0.054 | <.0001 |

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cardiac effects of medications such as ACE inhibitors used in conjunction with corticosteroids. Although a randomized controlled trial would be the most definitive method to evaluate the full benefits of corticosteroid use on cardiac function, this design would be ethically problematic because corticosteroid treatment of muscle weakness is the standard of care for boys with DMD. Trials that examine different dosing regimens, alone or in combination with cardiac medications, would be feasible. Until the time that results of such trials become available, consideration should be given to continuation of corticosteroid treatment after loss of ambulation because of its possible benefit in maintaining normal cardiac function and preventing other complications of DMD.

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References

Figure 1. Inclusion/exclusion criteria for regression analyses. Male MD STARnet patients born between 1982 and 2005 and followed through October, 2010, Arizona, Colorado, Georgia, Iowa, and western New York.