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

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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