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Use of Corticosteroids in a Population-Based Cohort of Boys With Duchenne and Becker Muscular Dystrophy

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Abstract

The use of corticosteroids for treatment of Duchenne and Becker muscular dystrophy in clinical practice from 1991 through 2005 was reviewed in a large population-based cohort (MD STARnet) of boys in 4 regional sites and 6 clinics of the United States. Corticosteroid use increased from 20% (11 of 56 individuals) in 1991 to 44% (93 of 218 individuals) in 2005. Average use varied by site and ranged from 15% to 49%. The median age of corticosteroid initiation was 6.9 years (range, 3.7–17.4 years). Dosage and growth information was available for 102 participants and showed a median dose as 0.729 mg/kg for prednisone and 0.831 mg/kg for deflazacort. T. The most common reasons that corticosteroids were discontinued included weight gain, behavioral side effects, and loss of ambulation, resulting in full-time wheelchair use. Substantial variations in clinical practice were identified among study sites.

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Keywords

Duchenne muscular dystrophy; corticosteroids; population-based studies; Becker muscular dystrophy

Duchenne and Becker muscular dystrophy are allelic neuromuscular disorders that form a spectrum of clinical severity resulting from variable effects on the integral muscle protein dystrophin. They are often referred to collectively as dystrophinopathies. Duchenne and Becker muscular dystrophy are X-linked recessive disorders with an estimated incidence of 1:3500 live male births¹ and are characterized by a progressive weakness of skeletal muscle.² The dystrophinopathies are caused by an abnormal amount or quality of the dystrophin protein, a key component of the sarcolemmal dystrophin-glycoprotein complex.^{3–6}

Many pharmacological treatments have been studied for Duchenne and Becker muscular dystrophy,^{4,5} but only corticosteroids such as prednisone and deflazacort have been shown to improve and/or preserve functional status.^{7–12} The clearest benefit of these medications is the improvement of muscle strength and the preservation of independent ambulation by 2 to 3 years.^{13–17} The recently published American Academy of Neurology Practice Parameter, *Corticosteroid Treatment of Duchenne Dystrophy*, recommends offering corticosteroids (prednisone 0.75 mg/kg/d or deflazacort 0.9 mg/kg/d) to all individuals with Duchenne and Becker muscular dystrophy.¹⁸ The Practice Parameter also recommends that treated individuals be monitored for side effects, including weight gain, behavioral changes, gastrointestinal complications, blood pressure changes, glucosuria, acne, and hirsutism.¹⁹

The Muscular Dystrophy Surveillance, Tracking, and Research Network (MD STARnet) is a population-based surveillance system funded by the Centers for Disease Control and Prevention to identify individuals with Duchenne and Becker muscular dystrophy born since 1982 and who resided in one of the participating sites (Arizona, Colorado, Iowa, and western New York). For this investigation, we examined 2007 MD STARnet data to evaluate the clinical use of corticosteroids among boys with Duchenne and Becker muscular dystrophy from 1991 through 2005. The findings of this report have implications for practice improvement in the treatment of individuals with Duchenne and Becker muscular dystrophy.

Methods

Potential Duchenne and Becker muscular dystrophy cases were identified through multiple case finding techniques (e.g., review of ICD-9 codes, neuromuscular clinic rosters). Medical records of potential cases were abstracted by trained abstractors, using a computerized abstraction instrument to record detailed clinical information from each case individual. Each individual was assigned a case status (definite, probable, possible, female, asymptomatic, or not Duchenne and Becker muscular dystrophy), using key clinical and diagnostic testing information from the abstracted medical record. These diagnostic elements were reviewed by a Clinical Review Committee of 4 neuromuscular clinicians, using defined criteria to classify cases. A full description of the MD STARnet surveillance methodology has been published previously.²⁰ Information collected on corticosteroid use included corticosteroid name, dose, and frequency; start and stop dates; and recorded

reasons for changing dose or stopping corticosteroids. Each study site maintains Institutional Review Board approval for this research.

The study population for this investigation included 428 males with a clinical diagnosis of Duchenne and Becker muscular dystrophy and who met the case definition criteria for “definite” or “probable” Duchenne and Becker muscular dystrophy. Each of these individuals had previously received a clinical diagnosis of Duchenne and Becker muscular dystrophy from a physician with expertise in the diagnosis and treatment of Duchenne and Becker muscular dystrophy. Eligible cases for this analysis had the following criteria: birth year from 1984 through 1998, documented residence within an MD STARnet site some time from 1991 through 2005, a clinical diagnosis of Duchenne and Becker muscular dystrophy, and complete information about corticosteroid use for the years 1991 to 2005.

Initially, each case record was reviewed to determine if it met the inclusion criteria. A case was classified as a resident for each year there was documentation of residence or clinical activity within a MD STARnet site. An individual who died at any point in a calendar year was included in the counts for that year.

Cases were classified as a corticosteroid user if they had documentation of corticosteroid use for at least 2 months from 1991 through 2005. If a case had corticosteroids prescribed in any part of a year and was on corticosteroids for at least 2 months, then that year was counted even if the 2 months fell across 2 different years. Annual percentage of corticosteroid users was calculated by dividing the number of patients on corticosteroids (as defined above) by the total number of eligible cases (as defined by the inclusion criteria) for that year.

We completed a secondary analysis using a narrow age range of cases to assess whether any patterns found in corticosteroid use were an artifact of the increasing mean age of the cohort or a true trend. We calculated the percentage of 5- to 9-year-olds with documented corticosteroid use during 3 time periods—1991 to 1995, 1996 to 2000, and 2001 to 2005—to examine the change in percentage of corticosteroid users between the 3 time periods.

For the current data presentation, cases were categorized by MD STARnet regional sites (coded as A, B, C, and E) and primary clinic (coded as 1 through 6). The designation of primary clinic site for each case was based on the predominant clinic attended for medical visits. Most participants were associated predominately with 1 clinic; however, those who attended 2 clinics equally were grouped in a separate category as “multiple.” Because the number of cases in the multiple category was very small ($n = 6$), we did not include this group in comparison analyses by clinic site.

Corticosteroid dose was calculated using the prescribed dose and frequency and the corresponding weight for that time period to determine the dose in milligrams per kilogram. The median age of corticosteroid initiation was determined by using the case age at the first documented use. Duration of use was calculated for all cases with a corticosteroid stop date and was calculated by subtracting the start date from the stop date to get a time value in months. All statistical analyses were conducted with SAS software.²¹

Results

Of the 428 cases of Duchenne and Becker muscular dystrophy identified by MD STARnet, 72 were excluded due to a birth year before 1984 or after 1998, and 5 were excluded because of incomplete data on corticosteroid use. Among this group of 351 boys, 179 (51.1%) had ever taken corticosteroids, with a median age of initiation of 6.9 years (range, 3.7–17.4) and a median duration of use of 41.0 months (Table 1). The percentage of cases that used corticosteroids increased from 19.6% in 1991 to 44.1% in 2005, but the increase was not steady during the 15-year period (Figure 1).

We calculated the percentage of 5- to 9-year-old cases with documented corticosteroid use during three 5-year time periods—1991 to 1995, 1996 to 2000, and 2001 to 2005—to determine if the observed increase in corticosteroid use represented a true trend or could be explained by the aging cohort. Results indicated that the percentage of 5- to 9-year-olds on corticosteroids increased from 35.3% to 47.1% for the entire cohort, although the change varied by site (Table 2).

The most common corticosteroid prescribed was prednisone, followed by deflazacort and prednisolone. The percentage of cases that used corticosteroids in 2005 ranged by site from 29.0% to 63.1% (Figure 1), and the percentage of cases that used corticosteroids in 2005 ranged by clinic from 80.2% at clinic 6 to 8.4% at clinic 5 (Figure 2). Dosage and growth information was available for 102 participants and showed a median dose for prednisone and prednisolone as 0.729 mg/kg and 0.831 mg/kg for deflazacort.

Among documented reasons for discontinuation, the most common were weight gain (23.3%), behavioral side effects (19.1%), and loss of ambulation, resulting in full-time wheelchair use (15.8%). The reason for discontinuing corticosteroids was unknown in 20.0% (Table 3).

Among the 179 corticosteroid users, corticosteroid dose or frequency of dose was altered 490 times. In most circumstances (56.7%), the reason for the alteration was not documented in medical records. The most common documented reason for changing corticosteroid dose (9.4%) was an increase in dose to adjust for weight change as the child grew. However, decreases in dose were also documented for indications such as weight gain (8.0%), behavioral side effects (6.5%), or a parent's request (2.2%) (Table 3).

There were 53 individuals who were offered corticosteroids and declined, including 13 who were offered and declined more than once. Five individuals initially declined but at another point in time consented to corticosteroid use. It is unknown why most individuals declined to take corticosteroids (85.2%), but the most common documented reason was parental choice or presence of a comorbidity.

Discussion

This study documents the clinical use of corticosteroids in a population-based sample of individuals with Duchenne and Becker muscular dystrophy. We identified an increase in corticosteroid use among MD STARnet cases during the period 1991 through 2005. Despite

this increased use, only about 50.9% of individuals in this cohort have ever been on corticosteroids. The reasons for this relatively low frequency of use are not well understood, but the data do show substantial variation among the clinical sites that were studied.

A pattern of steadily increasing corticosteroid use was found at each site except site A, which showed a decline from 2001 to 2005 (Table 2). This decline might have been due to the small number of 5- to 9-year-old cases identified at site A during this time period.

There was wide variation in corticosteroid use from an annual mean percent of 8.4% to 80.2% across individual clinics. The variation in physician prescribing practices appears to be a strong determinant of corticosteroid usage in our cohort, but the reasons for this variation cannot be determined from this analysis.

The MD STARnet case definition criteria do not differentiate between Duchenne and Becker muscular dystrophy but instead focus on the presence of dystrophinopathy; therefore, our analysis included some individuals with Becker muscular dystrophy. There is ongoing controversy about the use of corticosteroids to treat boys with Becker muscular dystrophy, and the inclusion of these cases may have increased the median age at initiation and/or decreased the percentage of cases using corticosteroids.

There have been no published studies examining the optimal age to begin corticosteroid treatment.¹⁷ However, most guidelines recommend initiation between 4 and 6 years of age.²² The median age of initiation in this cohort was 6.9 (range, 3.7–17.4). Future analyses will be necessary to determine if the median age of initiation decreases with new standards and practices involving corticosteroid use in individuals with Duchenne and Becker muscular dystrophy.¹⁸

The American Academy of Neurology Practice Parameter, *Corticosteroid Treatment of Duchenne Dystrophy*, recommends that corticosteroids be given at a dose of 0.75 mg/kg/d for prednisone or 0.9 mg/kg/d for deflazacort.¹⁸ The MD STARnet patients who were started on daily doses of prednisone and deflazacort closely followed the recommendations.

This study found that the most common side effects of corticosteroids were excessive weight gain and behavioral changes. This parallels other studies, which found that the most common side effects were weight gain and development of a cushingoid facial appearance 6 to 18 months after treatment.^{19,23,24} Normal growth and development, excessive weight gain, and behavioral changes were the primary reason for changes in dosage.

In conclusion, the beneficial effects of corticosteroid treatment on muscle strength and function in boys with Duchenne muscular dystrophy are well documented.¹⁸ Despite these benefits, many affected individuals do not appear to be receiving treatment. The reasons for this disparity are not well understood, but physician practice patterns, concerns about negative side effects, and other issues of patient and family preference all appear to play a role. The efforts of public health programs, neuromuscular specialty organizations, and parent support and advocacy groups are increasingly directed toward raising awareness and standardizing protocols for corticosteroid treatment. Ongoing public health monitoring will

be required to assess the impact of these treatment recommendations on the use of corticosteroids for boys with Duchenne and Becker muscular dystrophy.

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References

- Emery AE. Population frequencies of inherited neuromuscular diseases: a world survey. *Neuromuscul Disord.* 1991; 1(1):19–29. [PubMed: 1822774]
- van Essen, AJ., Verheij, JBG.M., Reefhuis, J., et al. [Accessed May 10, 2009] The natural history of Duchenne muscular dystrophy: analysis of data from a Dutch survey and review of age related events. Online Leyden Muscular Dystrophy pages. 2004. <http://www.dmd.nl/>
- Drachman DB, Toyka KV, Myer E. Prednisone in Duchenne muscular dystrophy. *Lancet.* 1974; 2(7894):1409–1412. [PubMed: 4140328]
- Fenichel GM, Brooke MH, Griggs RC, et al. Clinical investigation in Duchenne muscular dystrophy: penicillamine and vitamin E. *Muscle Nerve.* 1988; 11(11):1164–1168. [PubMed: 3067086]
- Mendell JR, Griggs RC, Moxley RT, et al. Clinical investigation in Duchenne muscular dystrophy: IV. Double-blind controlled trial of leonine. *Muscle Nerve.* 1984; 7(7):535–541. [PubMed: 6399927]
- Moxley RT III, Brooke MH, Fence GM, et al. Clinical investigation in Duchenne dystrophy: VI. Double-blind controlled trial of nifedipine. *Muscle Nerve.* 1987; 10(1):22–33. [PubMed: 3550455]
- 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):843–850. [PubMed: 16244521]
- Biggar WD. Duchenne muscular dystrophy. *Pediatr Rev.* 2006; 27(3):83–88. [PubMed: 16510548]
- Biggar WD, Gingras M, Fehlings DL, Harris VA, Steele CA. Deflazacort treatment of Duchenne muscular dystrophy. *J Pediatr.* 2001; 138(1):45–50. [PubMed: 11148511]
- 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): 249–255. [PubMed: 16545568]
- Fenichel GM, Florence JM, Pestronk A, et al. Long-term benefit from prednisone therapy in Duchenne muscular dystrophy. *Neurology.* 1991; 41(12):1874–1877. [PubMed: 1745340]
- King WM, Ruttencutter R, Nagaraja HN, et al. Orthopedic outcomes of long-term daily corticosteroid treatment in Duchenne muscular dystrophy. *Neurology.* 2007; 68(19):1607–1613. [PubMed: 17485648]
- Brooke MH, Fenichel GM, Griggs RC, et al. Clinical investigation of Duchenne muscular dystrophy: interesting results in a trial of prednisone. *Arch Neurol.* 1987; 44(8):812–817. [PubMed: 3632393]

14. Escolar DM, Scacheri CG. Pharmacologic and genetic therapy for childhood muscular dystrophies. *Curr Neurol Neurosci Rep*. 2001; 1(2):168–174. [PubMed: 11898513]
15. Wong BL, Christopher C. Corticosteroids in Duchenne muscular dystrophy: a reappraisal. *J Child Neurol*. 2002; 17(3):183–190. [PubMed: 12026233]
16. van Essen AJ, Kneppers AL, van der Hout AH, et al. The clinical and molecular genetic approach to Duchenne and Becker muscular dystrophy: an updated protocol. *J Med Genet*. 1997; 34(10): 805–812. [PubMed: 9350811]
17. Yilmaz O, Karaduman A, Topaloglu H. Prednisolone therapy in Duchenne muscular dystrophy prolongs ambulation and prevents scoliosis. *Eur J Neurol*. 2004; 11(8):541–544. [PubMed: 15272899]
18. Moxley RT III, Ashwal S, Pandya S, et al. Practice parameter: corticosteroid treatment of Duchenne dystrophy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. *Neurology*. 2005; 64(1): 13–20. [PubMed: 15642897]
19. Griggs RC, Moxley RT III, Mendell JR, et al. Duchenne dystrophy: randomized, controlled trial of prednisone (18 months) and azathioprine (12 months). *Neurology*. 1993; 43(3 pt 1):520–527. [PubMed: 8450994]
20. Miller LA, Romitti PA, Cunniff C, et al. The Muscular Dystrophy Surveillance Tracking and Research Network (MD STARnet): surveillance methodology. *Birth Defects Res A Clin Mol Teratol*. 2006; 76(11):793–797. [PubMed: 17036307]
21. SAS Institute, Inc. SAS 9.1.3 Help and Documentation. Cary, NC: SAS Institute, Inc; 2000–2004.
22. Manzur AY, Kinali M, Muntoni F. Update on the management of Duchenne muscular dystrophy. *Arch Dis Child*. 2008; 93:986–990. [PubMed: 18667451]
23. Griggs RC, Moxley RT III, Mendell JR, 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):383–388. [PubMed: 2012511]
24. Mendell JR, Moxley RT, Griggs RC, et al. Randomized, double-blind six-month trial of prednisone in Duchenne's muscular dystrophy. *N Engl J Med*. 1989; 320(24):1592–1597. [PubMed: 2657428]

Figure 1.
Annual percentage of MD STARnet cases that used corticosteroids, 1991–2005.

Figure 2.
Percentage of MD STARnet cases that used corticosteroids, by clinic, 1991–2005.

Percentage of MD STARnet Cases Ever on Corticosteroids and Age in Years at Corticosteroid Initiation, by Site, 1991–2005

Table 1

Site	Percentage of Cases Ever on Corticosteroids			Age in Years at Corticosteroid Initiation			
	Total (n)	Ever on Corticosteroids (n)	%	Total (n)	Median	Min	Max
A	97	49	50.5	48	7.1	3.7	11.0
B	65	35	53.8	34	7.5	3.8	17.4
C	116	47	40.5	46	7.5	4.0	15.3
E	73	48	65.7	47	6.1	3.9	13.7
Total	351	179	51.0	175	6.9	3.7	17.4

Table 2
Percentage of 5- to 9-Year-Old MD STARnet Cases Who Were Corticosteroid Users, by Site and Time Period, 1991–2005

Site	1991–1995			1996–2000			2001–2005		
	Total	Corticosteroid Users	%	Total	Corticosteroid Users	%	Total	Corticosteroid Users	%
A	36	14	38.9	50	21	42.0	31	6	19.4
B	16	7	43.8	29	14	48.3	31	17	53.1
C	30	2	6.7	45	4	8.9	39	24	53.3
E	32	17	53.1	39	23	59.0	28	17	63.0
Total	114	40	35.1	163	62	38.0	129	64	47.4

Table 3

Reasons for Discontinuing or Changing Corticosteroid Dose Among MD STARnet Cases, 1991–2005

Discontinuing Corticosteroids (n = 150)		Changing Corticosteroid Dose (n = 490)	
n	Reason	n	Reason
42	Unknown	278	Unknown
28	Weight gain	67	Other
23	Behavior	46	Increase in height and weight (regular growth pattern)
19	Wheelchair use	39	Weight gain
6	Other comorbidity	32	Behavior
5	Weight gain and behavior	11	Parent initiated
4	Upset stomach	9	Progressive muscle weakness
17	Other (ie, acne, itching, etc)	8	Wheelchair use