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CORTICOSTEROIDS AND DUCHENNE MUSCULAR DYSTROPHY: DOES EARLIER TREATMENT REALLY MATTER?

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In this issue of *Muscle and Nerve*, Merlini and colleagues report a prospective, long-term, open label study of low-dose, alternate-day corticosteroids starting in boys aged 2–4 years with Duchenne muscular dystrophy (DMD).[1] This is an interesting, very important observation, and we applaud the authors for their careful, objective observations and 14 years of follow-up. Their results showed that 4 out of 5 boys who started corticosteroids early (ages, 2.4 to 4.0 years) did better than those whose families opted for later initiation or no treatment.[1] It is striking that these boys, all with frame shift mutations consistent with DMD, continued ambulation beyond age 16 years. Before molecular genetic testing and quantitative dystrophin analysis in muscle, this functional milestone was diagnostic for Becker muscular dystrophy (BMD).[2]

The long-term benefits of corticosteroids in DMD are now well established.[3] In the Cooperative International Neuromuscular Research Group (CINRG) DMD natural history study of 340 boys followed prospectively, long-term corticosteroid use was associated with prolonged ability to stand from supine, stand from a chair, and ambulate without support, and there was improved pulmonary function and better upper limb function in adulthood.[4] It has long been assumed that corticosteroids might be more effective if they are started earlier, before significant muscle pathology is present. At age 5 years, the time most boys are diagnosed with DMD, considerable functional impairment already exists. Unfortunately corticosteroids do not appear to bring back lost function. Thus there is some imperative to develop better ways to diagnose DMD earlier, including newborn screening. The data in the study by Merlini et al. further supports this concept, which is also bolstered by emerging "genotypically personalized" treatments. This includes nonsense suppression therapies for boys with premature stop codon mutations, and exon-skipping by means of antisense oligonucleotides and modified morpholinos.[5–8] These treatments will likely yield more benefits if they are started as early as possible.[5–8]

Most corticosteroid studies have been performed in DMD subjects aged 5 years and older, when timed function testing and strength testing may be performed more reliably. Clinical trials in younger boys with DMD require the use of developmental functional milestones as outcome measures and are very challenging. The Centers for Disease Control (CDC) recently sponsored a DMD Care Considerations Working Group to address these questions.[3] This group did not recommend corticosteroid treatment for boys still gaining motor skills, particularly if under they are 2 years of age. Most boys with DMD continue to improve motor skills until age 4–6 years, at which time the CDC group recommends discussing corticosteroids with caregivers in anticipation that motor skills will soon plateau.[3,9] Once this occurs, typically at age 4–8 years, the group recommended initiating corticosteroids if known contraindications are not present. While many practitioners favor a more aggressive approach, with earlier initiation of treatment, there were no published data to support this.[3] Despite this study, a randomized, controlled trial or open parallel group design study will ultimately be required to truly ascertain the best age for initiation of corticosteroid treatment in boys with DMD. Regardless, this report presents a novel, potentially efficacious treatment protocol which may form the basis for future prospective studies.

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The Merlini et al. report poses additional questions as well. First, what is the role of genotype or genetic polymorphisms in explaining the significant outcome disparities in individuals with similar treatments? Three patients in the series by Merlini et al. had frame shift mutations on molecular genetic testing, yet they continued to ambulate past the age of 16–18 years, an unexpected phenotype for out of frame mutations. Exceptions to the reading-frame hypothesis may occur in up to 10% of DMD mutations.[10] There are reports of boys with DMD, documented by complete absence of dystrophin on muscle biopsy, who maintained ambulation past adolescence without corticosteroid treatment. In an open-label study using an antisense oligonucleotide (PRO-051, Prosensa) for exon 51 skipping, one boy with DMD had an extension phase baseline 6-min walk distance (6MWD) value of 647 meters at 10.3 years of age.[11] This 6MWD value was 104% of predicted control value for 6MWD, despite no recent treatment with the antisense oligonucleotide.[12] This performance was significantly discrepant from all other 6MWD values measured at baseline in the recent experience with the 6-min walk test (6MWT) in 174 DMD boys enrolled in the multicenter ataluren clinical trial.[13] Despite a complete absence of dystrophin, this boy in the PRO-051 extension phase trial was functioning far better than his aged-matched peers with DMD.

Genetic polymorphisms may also impact ambulatory outcomes in DMD.[14] Most neuromuscular specialists encounter outlier DMD patients who have significant prolongation of ambulation despite not receiving corticosteroids. Yet, given that 4 of 5 early corticosteroid-treated DMD subjects in this study maintained ambulation past age 16 years, genetic polymorphisms are most likely not a primary explanation for this observation. We previously reported a patient with DMD who still ambulated at age 20 years yet had a maternal uncle with an identical out of frame deletion mutation who died at age 19 years from respiratory failure.[15] Our patient received frequent pulse prednisone therapy for severe asthma from age 3 to 17 years, which was likely responsible for the difference in outcomes, rather than genetic polymorphism. Regardless, genetic and environmental factors will continue emerging as factors that could alter disease progression in DMD.

Importantly, shortened stature and delayed puberty appear to be the most significant side effects of early corticosteroid treatment.[3,4] Merlini and colleagues also documented permanent linear growth retardation (3.01–4.77 SD below population-based normative data).[1] A prior study reported that shorter stature in boys with DMD portended a better clinical course.[16] This could partially explain the findings in the present study. Natural history studies suggest that short stature is an under-recognized phenotypic feature of DMD, which is seen in untreated individuals with normal hormonal levels and bone age.[17–19] The prevalence of short stature increases during childhood and adolescence. By age 18 years, most boys with DMD fall below the 5th percentile for height.[9]

In the contemporary CINRG natural history study, no boy with DMD less than age 4 years ($n = 17$) had short stature (standing or calculated height less than two standard deviations below normal).[4] At baseline, 258 subjects (76%) were currently or previously treated with corticosteroids after age 4 years. Yet, the proportion of participants in this cohort with short stature increased with age and duration of follow-up. Among 13 to 18 year olds, the proportion of short statured DMD participants increased from 25/80 (31.2%) to 34/77 (44.1%) after 24-months. Additionally, 48 (14%) ambulatory DMD boys became nonambulatory within 12-months of study enrollment, and 12 (25%) of them met criteria for short stature. The mean age at loss of ambulation among short statured boys was significantly greater than for those with normal height (14.8 ± 2.9 years vs. 11.2 ± 2.4 years respectively, $P = 0.001$) (Mah JK, unpublished data; presented at the 3rd Endocrinology in DMD conference, Dec 2, 2011, Toronto, Ontario). The prolongation of ambulation and later age for transition to wheelchair among short statured boys with DMD in the CINRG natural history study approached that described in the report by Merlini et al.[1]

Alternatively, long-term, continued corticosteroid administration may be the critical factor for slowing disease course in DMD rather than earlier age at treatment initiation. Short stature may be a biomarker for the efficacious effect of corticosteroids on other disease-ameliorating mechanisms in DMD, such as the NF-Kappa B pathway.[20] Short stature might be an indicator that corticosteroids are having an effect on disease ameliorating mechanisms. Prospective studies that compare long term functional outcomes following initiation of corticosteroids in boys with DMD with varying degrees of linear growth retardation would elucidate the interdependent roles of height and corticosteroids. The determination of the independent role of height (with potential impact on biomechanical and metabolic efficiency during gait) will be further enhanced by studies of noncorticosteroid treated boys with DMD, comparing outcome endpoints such as timed function tests and level of ambulation in those with and without short stature. Moreover, previous studies suggest that

deflazacort may have less weight gain side effects compared to prednisone.[21] Given the severe degrees of short stature observed in this study, the relative impact on linear growth of prednisone vs. deflazacort also merits further investigation.

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