Long-Term Outcome of Interdisciplinary Management of Patients with Duchenne Muscular Dystrophy Receiving Daily Glucocorticoid Treatment

Brenda L. Wong, MD[1], Irina Rybalsky, MD, PhD[1], Karen C. Shellenbarger, RN, APRN, CPNP[1], Cuixia Tian, MD[1], Mary A. McMahon, MD[1,2], Meilan M. Rutter, MD[1,3], Hemant Sawnani, MD[1,4], and John L. Jefferies, MD[1,5]

Objective To evaluate clinical outcomes and steroid side effects in a cohort of patients with Duchenne muscular dystrophy (DMD) treated with long-term daily glucocorticoid therapy. Although daily glucocorticoid therapy has been shown to extend ambulatory function in DMD, less frequent dosing is often used because of side effect concerns.

Study design Retrospective study of 97 patients with DMD aged 10 to <16 years treated with daily glucocorticoid (89% on deflazacort) for a mean of 8.5 years. Outcome measures were motor, pulmonary, and cardiac function, and scoliosis. Side effects were growth failure and weight gain, facial fullness, blood pressure, bone health, cataracts, gastrointestinal symptoms, behavior, hypertrichosis, and need for medication interventions.

Results For 13- to 16-year-old patients, 40% could rise from the floor and 50% could perform the 30-foot run test. Forced vital capacity for the entire cohort was well preserved. Thirteen percent of younger (10- to <13-year-old) and 21% of older patients had findings of left ventricle systolic dysfunction. Six percent (all aged 16 years) developed scoliosis (Cobb angle >20 degrees). Eighty-six percent had normal weight velocities; 30% had no increased facial fullness; 72% had short stature; and 19% had asymptomatic cataracts. Asymptomatic spine compression deformities were noted in 76% and long bone fractures in 30%. One patient stopped glucocorticoid because of behavioral concerns.

Conclusions With evidence for improved outcomes and manageable side effects, we recommend use of daily glucocorticoid therapy for patients with DMD with anticipatory management of side effects and a coordinated interdisciplinary care approach. *(J Pediatr 2017;182:296-303).*

Duchenne muscular dystrophy (DMD) is estimated to affect 1 in 3500 male births.[1] This disease results from deficiency of the protein, dystrophin, and is characterized by muscle weakness in early childhood, loss of ambulation between ages 7 and 13 years, and premature death typically by the early 20s because of progressive cardiorespiratory failure.[1-3] Glucocorticoid therapy has consistently been shown to stabilize muscle function and slow disease progression, although long-term benefits vs risks of severe side effects are unclear.[2,4]

In 1974, Drachman et al[5] reported a beneficial effect of prednisone in patients with DMD, evidenced by prolonged ambulation and improved motor function for up to a year or longer, yet resultant side effects (ie, Cushingoid facies, excessive weight gain) were concerning. Subsequent trials in the 1980s and 1990s largely corroborated this, but side effects of glucocorticoid hindered its widespread adoption.[4,6] Studies of deflazacort, an oxazoline derivative of prednisone, indicated that daily treatment maintained muscle function and spinal alignment with less weight gain compared with prednisone, although deflazacort therapy was associated with more asymptomatic cataracts.[7] Follow-up research suggested that deflazacort therapy was associated with spine compression fractures, growth failure, and moderate weight gain, yet the clinical improvements in cardiopulmonary function, ambulation, and gross motor function reinforced its benefits for patients with DMD.[3,4,8] Taken together, studies of glucocorticoid therapy in DMD show the need for proactive treatment strategies to monitor and mitigate the side effects of glucocorticoids.[9] A multidisciplinary approach to disease management is recommended as best practice for DMD care.[2,10] In 2010, Moxley et al[2] described appropriate management as including neuromuscular, orthopedic, rehabilitation, pulmonary, cardiac, gastrointestinal, and psychosocial care, in addition to regular review of the benefits and side effects of long-term glucocorticoid therapy. The same year, Bushby et al[10,11] provided US Centers for Disease Control and Prevention Care Consideration guidelines that recommended rigorous and standardized management for the predictable side effects of glucocorticoid to maximize benefits.

The Comprehensive Neuromuscular Center (CNC) at Cincinnati Children's Hospital Medical Center (CCHMC) is a level 3 National Committee of Quality

BMD	Bone mineral density	EHRs	Electronic health records
CCHMC	Cincinnati Children's Hospital Medical Center	FVC	Forced vital capacity
		GH	Growth hormone
CNC	Comprehensive Neuromuscular Center	MEP	Maximal expiratory pressure
		MIP	Maximal inspiratory pressure
DMD	Duchenne muscular dystrophy	NSAA	North Star Ambulatory Assessment

From the [1]Comprehensive Neuromuscular Center; [2]Division of Physical Medicine and Rehabilitation; [3]Division of Endocrinology; [4]Division of Pulmonary Medicine; and [5]The Heart Institute, Cincinnati Children's Hospital Medical Center, Cincinnati, OH

The authors declare no conflicts of interest.

http://dx.doi.org10.1016/j.jpeds.2016.11.078

Assurance-recognized Patient Centered Specialty Practice that has provided interdisciplinary care to a DMD population of about 700 patients since 2005. Within this care model, CNC patients receive treatment from providers in the core disciplines of neurology, cardiology, pulmonology, endocrinology, physical therapy and rehabilitation, and nutrition in a shared clinic setting. Patients may also receive consultative services.

As clinical outcomes in chronic disorders with multiple system complications like DMD are largely linked to the care model employed, outcomes research may inform both clinical best practice guidelines and the design of future clinical research studies. Here, we evaluate and report the long-term outcomes of coordinated, collaborative, interdisciplinary patient- and family-centered care for a large cohort of patients with DMD receiving long-term daily glucocorticoid therapy, the majority of whom (89%) were on daily deflazacort.

Methods

Participants were males aged 10 to <16 years (at the most recent clinic visit) diagnosed with DMD and managed with a coordinated care program by an interdisciplinary team of providers at the CCHMC CNC. We recommend daily prednisone (starting dose 0.75 mg/kg/day) or deflazacort (0.9 mg/kg/day) to treat boys with DMD after the diagnosis has been made, with a balanced discussion of benefits and risks of treatment.[12] Because of the inability to monitor motor responses (timed rise from the floor, run 30 feet/10 meter, climb 4 steps, North Star Ambulatory Assessment [NSAA]) for boys younger than age 3 years, and the concern for growth arrest at very young ages of <3 years, we initiate prednisone/deflazacort around age 3 years or older. As glucocorticoid therapy confers definite benefit for motor function, cardiac and pulmonary health, and spine curvature, our care protocol is to manage the side effects with counseling and interventions for growth and nutrition, treatment of exacerbation of behavior difficulties with or without dose reduction, and not discontinue glucocorticoid therapy unless parents decide that the side effects outweigh the benefits.

Participants met the following inclusion criteria: a DMD clinical phenotype confirmed by DNA testing or lack of dystrophin on muscle biopsy, patients with clinic follow-up visits (to provide clinic data for study analyses), duration of long-term daily glucocorticoid use ≥3 years, age at first CNC visit ≤7 years, duration of follow-up ≥3 years, and most recent clinic visit between September 2011 and May 2015. Informed consent for compiling clinical data in an Institutional Review Board-approved neuromuscular database (2010-1881) was obtained.

We performed a retrospective review of electronic health records (EHRs) of patients who were included in the above-mentioned neuromuscular database to provide data for this analysis, as follows:

Motor function was assessed by functional mobility status, timed function tests, and the NSAA. Functional mobility status was based on a value assigned by the functional mobility scale, a measure with values from 1 (mild gait abnormalities) to 8 (unable to sit without support)[13] (**Figure 1**, A). Timed function tests included timed sit-to-stand (timed Gowers') and timed 30-foot run/walk tests. The NSAA is a 17-item measure of motor function in ambulant patients with DMD, with performance of tasks scored 0, 1, or 2 based on the presence of compensatory actions and ability to complete each task. The NSAA was completed by trained physical therapists; timed sit-to-stand, 30-foot run/walk, spine curvature, and range of joint movements (contractures) were evaluated by neuromuscular physicians.

Cardiac function was evaluated by electrocardiogram, echocardiogram, or cardiac magnetic resonance imaging. Outcome measures of interest included left ventricle ejection fraction and left ventricle fractional shortening. Resting blood pressure was obtained at each clinic visit.

Pulmonary function was evaluated by pulmonary function tests completed by trained technicians in the CCHMC pulmonary function test laboratory. Outcome measures of interest included forced vital capacity (FVC), FVC% predicted, maximal inspiratory pressure (MIP), MIP% predicted, maximal expiratory pressure (MEP), MEP% predicted, and cough peak flow.

Growth and weight gain were evaluated by height and weight percentiles, and presence of facial fullness/Cushingoid facies at every clinic visit. Standing height (cm) and weight (kg) were measured and entered into the EHR. Short stature was defined as height less than the third percentile for age. The presence of facial fullness or Cushingoid facies (unaffected, intermediate facial fullness, or Cushingoid facies) was graded by neuromuscular physicians (**Figure 2**). All patients were routinely screened for insulin resistance and hyperglycemia by fasting glucose and insulin serum concentrations, and glycosylated hemoglobin; those with abnormal screens, presence of acanthosis nigricans, and/or excessive weight gain despite dietary interventions were further tested for insulin resistance using an oral glucose tolerance test.

Bone health was evaluated by bone mineral density (BMD), presence of fractures, and vitamin D status. Lumbar spine (adjusted for height) and lateral distal femur BMD were assessed annually by dual energy x-ray absorptiometry. Fracture data was collected from review of the medical history, patient report, and annual spine radiographs. Vitamin D status was assessed by measuring 25-hydroxyvitamin D serum concentrations.

Scoliosis was screened by neuromuscular physicians by the forward bending test, followed by scoliosis radiographs for positive screens for spine asymmetry (Cobb angle >10 degrees). A Cobb angle >20 degrees was considered significant scoliosis. Contractures of the knees and ankles impact motor function for standing and walking. They are defined as loss of range-of-motion for full knee extension and loss of ankle dorsiflexion to neutral with knees extended. Range-of-motion for knee extension and ankle dorsiflexion with knees extended and flexed were measured at each clinic visit.

Cataracts were determined annually by trained ophthalmologists. Presence or absence of cataracts, as well as degree of severity (asymptomatic or symptomatic), were recorded.