Acta Myologica • 2012; XXXI: p. 16-20

The Canadian experience with long term deflazacort treatment in Duchenne muscular dystrophy

Laura C. McAdam[1 2], Amanda L. Mayo[3], Benjamin A. Alman[1 4 5], W. Douglas Biggar[1 2 5]

[1] Holland Bloorview Kids Rehabilitation Hospital, Toronto, Canada; [2] Department of Pediatrics, University of Toronto, Toronto, Canada; [3] Department of Medicine, Division of Physiatry, University of Toronto, Canada; [4] Department of Surgery, Division of Orthopaedics, University of Toronto, Toronto, Canada; [5] Hospital for Sick Children, Toronto, Canada

Deflazacort is the most commonly prescribed corticosteroid for the treatment of Duchenne muscular dystrophy in Canada. We review the long term experience with deflazacort treatment at two centers in Canada; Montreal and Toronto. Deflazacort has benefitted both cohorts by prolonged ambulation, preserved cardiac and respiratory function, less scoliosis and improved survival. Common side effects in both cohorts include weight gain, decreased height and cataract formation. The Canadian experience supports the use of deflazacort in treating boys with Duchenne muscular dystrophy.

Key words: Deflazacort, Duchenne Muscular Dystrophy, Canada

Introduction

Duchenne muscular dystrophy (DMD) is a congenital, chronic degenerative muscle disorder that results in loss of ambulation, respiratory compromise and cardiac dysfunction (1). Corticosteroids are the standard of care for the treatment of DMD (1-4). Prednisone, prednisolone and deflazacort are the corticosteroids used to treat DMD. Corticosteroids have been shown to prolong independent ambulation, improve pulmonary function, delay the onset of cardiomyopathy and reduce the incidence of scoliosis (1, 2, 5). Here we examine the Canadian clinical experience with deflazacort.

Deflazacort is an oxazoline derivative of prednisolone with anti-inflammatory and immunosuppressive activity (6, 7). The effect of deflazacort on the progression of symptoms in DMD as well as the side effect profile have been characterized (8-18). Compared to prednisone, deflazacort has been shown in other diseases to cause fewer side effects including better preservation of bone mass (19-22), less weight gain (19, 20, 22, 23), better lipid profile (20, 22, 24) and less glucose intolerance (24, 25).

A direct comparison of deflazacort and prednisone in DMD has been studied in a multicenter, double-blind, randomized trial of 18 patients over one year of treatment (14). There was no significant difference in motor outcomes however, there was less weight gain in the group treated with deflazacort compared to prednisone (2.17 kg *vs*. 5.08 kg) (14). Two patients developed small cataracts in the deflazacort group and none were observed in the prednisone group. Other side effects were equally distributed including behaviour changes, increased appetite, cushingoid appearance, hirsutism and gastric symptoms (14). There is an international study planned to compare two prednisone dosing schedules to daily deflazacort (26).

Biggar et al. (9) compared two different deflazacort protocols; one from Toronto (0.9 mg/kg daily) and one from Naples (0.6 mg/kg/d for the first 20 days of the month). Benefits were seen with both protocols, however, the higher daily dose, Toronto protocol, resulted in prolonged ambulation (77% at 15 years compared to 25% at 15 years) and patients were less likely to develop scoliosis (16% compared to 30%). However, 30% developed asymptomatic cataracts with the Toronto protocol compared to none with the Naples protocol. The mean weight was similar and remained between the 25th and 50th percentile for treated boys with both protocols at 9, 12 and 15 years. In the Naples control group, body weight was consistently 25% higher compared to the treated group. In the Toronto control group, the weight was the same as

Address for correspondence: Laura C. McAdam, Holland Bloorview Kids Rehabilitation Hospital, 150 Kilgour Road, M4G 1R8, Toronto, Ontario, Canada. E-mail: lmcadam@hollandbloorview.ca

the treated group at 9 years, increased compared to the treated group at 12 years and was less than the treated group at 15 years. Height was reduced for treated boys compared to controls in both protocols for 9 and 12 years. There was greater growth suppression in the Toronto protocol compared to the Naples protocol at 12 and 15 years. Pulmonary and cardiac function for the 2 protocols were not presented.

Members of the Canadian Pediatric Neuromuscular Group were surveyed to determine the current care of pediatric DMD patients across Canada (27). Deflazacort (0.9 mg/kg/d) was the corticosteroid prescribed at all centers. Two of the centers occasionally prescribe prednisone (0.75 mg/kg/d) (27). The care for individuals with DMD across Canada is relatively consistent and includes multidisciplinary teams, continuation of deflazacort treatment after loss of independent ambulation, routine calcium and vitamin D supplementation, and the use of night splints to maintain ankle dorsiflexion. All sites also include routine surveillance of pulmonary function, cardiac function (electrocardiogram and echocardiogram) and bone density scans. The standard of care is consistent with the recommendations from Bushby et al. (1, 2) regarding management of DMD.

Five articles have been published regarding Canadian clinical data evaluating the impact of deflazacort in DMD (8-12, 18). One paper has been submitted for publication (28). One Canadian paper is not included in this review because the data included boys with DMD treated with both prednisone and deflazacort (29). Montreal and Toronto are the two centers in Canada that have published their experience regarding the long term benefits of deflazacort in DMD (8-12, 18, 28). Houde et al. (11) published a retrospective review of 79 patients with DMD (Table 1). Biggar et al. (10) published an open label study of 74 patients with DMD (Table 1). Both cohorts of patients were started at a dose of 0.9 mg/kg/d of deflazacort, vitamin D (400 IU [11] or 1000 IU [10]) and elemental calcium (250 mg tid [11] or 750 mg daily [10]). The Toronto cohort recommended calcium and vitamin D to patients not treated with deflazacort (10).

Muscle strength

Muscle strength was preserved in both cohorts comparing treated patients to the control group. Muscle strength was measured differently at the two centers. In Montreal, they graded manual muscle testing according to the Medical Research Council Scale in 34 muscles. Scores were cumulated and converted to a percentage of normal. At 16 years of age patients treated with deflazacort had 63 ± 4% (n = 8) muscle strength compared to 31 ± 3% for control patients (n = 21) (11). In Toronto, they used functional measures of strength. Of treated patients, 28 of 40 could rise from supine to standing at 10 years of age, 15 of 31 at 12 years, 4 of 17 at 15 years and none of 6 at 18 years. For climbing 4 standard stairs (17 cm) with a railing, 28 of 40 could climb stairs at 10 years, 17 of 31 at 12 years, 6 of 17 at 15 years and 1 of 6 at 18 years (10).

Ambulation

Ambulation was prolonged in treated patients for both cohorts (Table 2). In both cohorts, control patients lost ambulation by 12 years (Montreal cohort 9.6 ± 1.4 yrs [n = 32] and Toronto cohort 9.8 ± 1.8 yrs [n = 34] [10, 11]). For treated patients in the Montreal cohort, 53% (13/23) were walking at 12 years of age (11). For treated patients in the Toronto cohort, 81% (25/31) were walking at 12 years, 76% (13/17) at 15 years and 33% (2/6) were walking at 18 years (10).

Cardiac and respiratory function

Cardiac and respiratory function were preserved in both cohorts (Table 3) (10-12).

Spinal alignment

Spinal alignment was preserved by deflazacort treatment (Table 4) (10, 11, 18). For the Montreal cohort, scol-

Table 1. General characteristics.

	Montreal		Toronto	
	Control	**Treated**	**Control**	**Treated**
Number	42	37	34	40
Age*	14.5 ± 2.8 yrs	13.1 ± 3.2 yrs	15.2 ± 2.5 yrs	15.2 ± 2.7 yrs
Treatment initiation*		7.6 ± 1.7 yrs		7.7 ± 1.2 yrs
Length of treatment*		5.5 yrs		5.5 yrs
Deflazacort dose* (mg/kg/d)		7.6 yrs; 0.9 13 yrs; 0.69 ± 0.22		7.7 yrs; 0.9 10 yrs; 0.8 ± 0.18 15 yrs; 0.55 ± 0.09 18 yrs; 0.5 ± 0.2

* Values are mean ± standard deviation (s.d.).

Table 2. Ambulation.

	Montreal		Toronto	
	Control	**Treated**	**Control**	**Treated**
Age of loss of ambulation (yrs ± s.d.)	9.6 ± 1.4 yrs n = 32	11.5 ± 1.9 yrs n = 12	9.8 ± 1.8 n = 34	Not calculated *

* 2 boys still ambulatory at 18 years.

Table 3. Cardiac and respiratory function.

	Montreal		Toronto	
	Control	**Treated**	**Control**	**Treated**
Age at Cardiac testing (yrs ± s.d.)	14.5 ± 3.8 n = 48	13.3 ± 4 n = 38	16 ± 2 n = 34	14 ± 2 n = 40
LVEF	46.0 ± 10%	52.9 ± 6.3%	58% LVEF < 45%	10% LVEF < 45%
Fractional Shortening	26.6 ± 5.7%	30.8 ± 4.5%	21 ± 8%	33 ± 7%
FVC % predicted	16 yrs (n = 21) 48 ± 22	16 yr (n = 8) 66 ± 14	10 yrs 65 ± 13% 15 yrs 47 ± 19% 18 yrs 34 ± 10%	10 yrs 95 ± 14% 15 yrs 88 ± 12% 18 yrs 81 ± 13%

iosis was defined as any spinal curve. The degree of scoliosis was less for the treated patients (14 ± 2.5°) compared to control patients (42 ± 24°) (11). The definition of scoliosis for the Toronto cohort was a curve > 20° (10). A Kaplan-Meier curve revealed significant preservation of spine alignment with deflazacort after 8 years of treatment (mean age 16) (18). There were fewer surgeries for scoliosis in the treated groups within both cohorts (Table 4) (10, 11).

Survival

Survival is prolonged with deflazacort treatment. In the Toronto control group, 12 of 34 (35%) died in their second decade (mean age 17.6 ± 1.7 yrs) secondary to cardiorespiratory complications (10). In the Toronto treated group, 2 of 40 (5%) died at 13 and 18 years due to left ventricular failure (10). Survival was not commented on for the Montreal cohort (11). Both cohorts were followed until 18 years.

Side effects

Fractures

With both cohorts, there were equal long bone fracture rates in the treated and control patients (Table 5) (10, 11). Additionally, there were 12 vertebral fractures recorded in 7 treated patients in the Montreal cohort, none in the control group (11). Vertebral fractures were not reported in the Toronto cohort (10).

Bone mineral density

Bone mineral density (BMD) was reported for the treated group from Montreal. The lumbar (L_1-L_4) Z-score declined with increased duration of treatment (-1.8 after 1 year, -4.5 after 7 years) (11). The Z-scores were age matched and not corrected for height. Bisphosphonates were started in 19 of the 37 patients; alendronate in 17 and pamidronate in 2 (11). For the Toronto cohort, the

Table 4. Spinal alignment.

	Montreal		Toronto	
	Control	**Treated**	**Control**	**Treated**
Scoliosis	28/42 (67%)	10/37 (27%)	30/34 (90%)	4/40 (10%)
Scoliosis surgery	12	0	30	4

Table 5. Fractures.

	Montreal		Toronto	
	Control	**Treated**	**Control**	**Treated**
Long bone fracture	11/42 (26%)	9/37 (24%)	25%	25%
Vertebral fracture	None recorded	7/37 (19%)	Not reported	Not reported

age-based L_1-L_4 Z-score at baseline (T_0) was -1.1 ± 1.8, height-adjusted BMD Z-score was -0.5 ± 0.8 (n = 39, age 6.6 ± 1.6 yrs) (28). At T_0 and all subsequent time points, the height-adjusted Z-scores were significantly higher than age-based Z-scores. Height-adjusted Z-scores remained stable with years of deflazacort until boys started losing ambulation. By contrast, and similar to the Montreal cohort, age-based Z-scores declined with years of deflazacort.

Weight

Weight excess for the Montreal cohort was defined as body mass index (BMI) > 85%. At 8 years of age, 3 of 18 control and 8 of 31 treated boys had a BMI > 85% for the Montreal cohort (11). At 12 years, 6 of 11 control and 13 of 21 treated had a BMI > 85%. The frequency of weight excess appeared similar for both treated and control groups at 12 years (62% *vs*. 55%) (11).

For the Toronto cohort, the mean weight for age in treated patients was between the 25 and 75th percentile between 10 and 18 years of age (10). For control patients, their weight was greater than the treated boys at 10 years (37 ± 6 kg *vs*. 34 ± 4 kg), slightly less at 15 years (52 ± 15 kg *vs*. 58 ± 6 kg) and then decreased to the 3-10 percentiles at 18 years while the treated group remained at the 50th percentile (53 ± 12 kg *vs*. 71 ± 8 kg) (10). Deflazacort delayed the weight loss phase of this disease. It is important to note that while BMI is a useful measurement in the general population it is difficult to interpret in this population due to their short stature. Percent body fat determined by subcapital total body DEXA could be a better measurement for obesity.

Height

Height was decreased in the treated group compared to the control group for both cohorts. In the Montreal cohort, there was decreased rate of growth where only 3 of 20 treated patients grew 4 cm/year or more compared to 19/19 in the control group (11). In the Toronto cohort, treated boys were significantly shorter than the control at 10 years age (128 ± 5 cm *vs*. 135 ± 6 cm), 15 years (143 ± 9 cm *vs*. 164 ± 8 cm) and 18 years (156 ± 7 cm *vs*. 166 ± 7 cm) (10). For the Toronto cohort, when the boys were ambulating, height was measured to the nearest 0.1 cm using a standiometer. When the boys were nonambulatory, the height was calculated based on their measured ulna length (30). None of the boys in either cohort were treated with growth hormone.

Cataracts

Cataracts were more common in treated patients in both cohorts (Montreal 49% [18 of 37] [11] and Toronto 55% [22 of 40] [10]). Most of the patients in Montreal (17/18) developed cataracts after at least 5 years of treatment (11). In the Toronto cohort, cataracts were noted as early as 4 months and as late as after 10 years of treatment (10). The patients on deflazacort are assessed annually by an Ophthalmologist (10). If the cataracts are interfering with vision in sunlight we recommend sunglasses and a brimmed hat. Six of the patients in the Toronto cohort had large central cataracts that required cataract surgery. Increased intraocular pressure has not been an issue.

Conclusions

Deflazacort is the most commonly prescribed corticosteroid in Canada (27). Longitudinal data have been published in 2 cohorts of DMD patients in Canada, Montreal and Toronto (8-12, 18). Deflazacort treatment benefitted both cohorts with prolonged ambulation, preserved cardiac and respiratory function, less scoliosis and improved survival. Common side effects reported include increased weight gain, decreased height and cataract formation. It is unclear how deflazacort affects bone health. Delayed puberty was not commented on. There were no reported problems with wound healing, increased bacterial or viral infections, diabetes or glucosuria. Standards of care across Canada are quite similar. The Canadian experience supports the use of deflazacort in treating boys with DMD.

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