ABSTRACT: The purpose of this long-term, open parallel-group, double-consent study of alternate-day, low-dose prednisone in 2–4-year-old patients with Duchenne muscular dystrophy (DMD) was to determine whether prednisone produces a beneficial effect when given earlier than usual. Muscle function was evaluated by timed tests, and muscle strength with a hand-held myometer. After 55 months of treatment, the five patients (mean age 8.3 years) in the prednisone group were still able to get up from the floor, whereas two of the three in the control group had lost this ability. Side effects included a decline in growth rate in the prednisone-treated patients and excessive weight gain in one control and three treated patients. Because steroids are effective in prolonging function, but not in recovering lost function, we propose that treatment be started with low-dose prednisone in DMD patients as soon as the diagnosis is definite.


EARLY PREDNISONE TREATMENT IN DUCHENNE MUSCULAR DYSTROPHY

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Duchenne muscular dystrophy (DMD) is a progressive disorder in which the ability to rise from the floor is lost between 7 and 9 years of age, the ability to walk is lost at a mean age of 9.5 years, and respiratory failure invariably occurs in the second decade.36 At present, DMD therapy is based on symptomatic treatment and supportive care. Convincing evidence for clinical efficacy is available only for steroids.13 Long-term steroid treatment in DMD was shown to prolong ambulation, stabilize muscle strength for periods of up to 3 years, and preserve pulmonary function.7,11,12,16,20,30 Given these positive effects of steroids in slowing disease progression, better results might be expected with earlier initiation of treatment. Nevertheless, only 4 patients, out of approximately 600 reported,3,7,11,12,16,17,20,21,30,32,38,41 were under 4 years of age at the beginning of treatment.11,12 This may be because, previously, a firm diagnosis of DMD required evidence of locomotor problems, which are noticed between the ages of 3 and 6 years.8 More recently, earlier diagnosis has become possible by neonatal screening,4,18,34,45 investigation of developmental delay,1 and, in presymptomatic young patients, evaluation of high serum creatine kinase (CK) levels discovered incidentally.13,22 Prolonged high-dose steroid treatment is effective in slowing the disease’s progression, but side effects include weight gain, cushingoid features, hypertension, hyperactivity, growth retardation, and cataracts.17,21 Reduction in the total amount of steroids with different treatment schedules, such as alternate-day,13,17,24 pulsed,10,38 high-dose intermittent,13 or daily low-dose administration,3,40 may decrease side effects, but their long-term efficacy in preserving muscle strength and function has not been proven.

Given the progressive nature of DMD, treatment is more effective the earlier it is started.13 Therefore, we conducted this study to: (1) determine whether prednisone has a beneficial effect in DMD children between 2 and 4 years old; (2) determine whether the alternate-day schedule is beneficial in the long
term; and (3) better assess the side effects of long-term treatment with prednisone.

MATERIALS AND METHODS

Patients and Inclusion Criteria. For this study we considered boys from 2 to 4 years old with high serum CK, absence of dystrophy upon muscle biopsy, vaccine cycle completed at least 2 months previously, and absence of specific contraindications for steroid treatment (immunodeficiency, cardiomyopathy, hypertension, glaucoma). Patients came to our attention because of a marked increase of serum CK discovered after incidental illness in the first year of life (patients 4, 5, 6, and 7), or in years 2–3. All children were considered normal by their parents. First steps occurred between the ages of 12–15 months in all but one, who walked at 18 months (patient 3). Gower’s sign was present in 5 patients (patients 1, 2, 3, 7, and 8). All were unable to run freely and had some difficulty in climbing stairs. The parents were allowed to choose to have their child in either the prednisone group or the control group, with the understanding that it was possible to interrupt or cross-over at any time. Parents signed an informed consent in the presence of an auditor witness. The institutional ethics committee of each center approved the protocol.

Trial Design. This was a prospective long-term, open parallel-group, double-consent study of low-dose (alternate-day) prednisone in 2–4-year-old patients with DMD. Patients were followed at the two collaborating institutions. After the initial evaluations, prednisone was started at 0.75 mg/kg daily for the first 2 weeks, then 1.25 mg/kg on alternate days. Patients were reassessed as outpatients three times in the first 3 months, and then as inpatients every 6 months. At each visit the principal investigator and the pediatric specialist performed independent clinical assessments and evaluated side effects.

Efficacy Measurements. Muscle function was evaluated by timed tests, including measurement of the time needed to stand up from a seated position on the floor with legs outstretched, climb six standard-size steps, and run or walk 10 m as fast as possible. An overall functional grade was assigned using Walton’s scale.36 Muscle strength was evaluated after the age of 5 years with a hand-held dynamometer (Type CT 3001, Citec, C.I.T. Technics BV, Groningen, The Netherlands). The strength of the elbow flexors, grip, and the knee flexors and extensors were measured on the child’s preferred side.31 Forced vital capacity (FVC) was also tested after the age of 5 years.

Safety Measurements. For each patient, clinical and laboratory analyses were carried out at months 0, 1, 3, and 6, and then every 6 months. Patients were examined and parents were interviewed for side effects, including fatigability, hunger, gastrointestinal problems, and behavioral changes. In addition, the occurrence of all incidental illnesses and medications, surgery, or other events were recorded at each examination. Blood tests included complete blood count, tests of hepatorenal and adrenal cortical function, and determination of serum CK and CK-MB, aldolase, glucose, calcium, phosphate, and immunoglobulin G, A, and M (IgG, IgA, and IgM).

Weight, height, pulse, and blood pressure were recorded at each visit. Weight was evaluated using body mass index (BMI) and body weight excess. BMI was calculated as weight (kilograms) divided by height (meters) squared, and the values were transformed into standard deviation scores (SDS) based on Rolland-Cachera standards.35 Body weight excess was calculated as patient weight minus ideal weight for statural age × 100/ideal weight. Normal standards from Tanner et al.13,44 were used. Height was measured with a wall-mounted Harpenden stadiometer (Harpenden, Ltd., Crymmych, Pembrokshire, Wales). Height SDS were calculated with the formula: patient’s height minus 50th percentile height for gender and age/standard deviation for gender and age. Normal standards from Tanner et al.13,44 were used.

Bone maturation was evaluated using hand radiographs, and bone age was estimated according to Greulich and Pyle.19 Bone mineral density (BMD) was measured with dual-energy X-ray absorptiometry (Model XR-36, Norland Medical Systems, Fort Atkinson, WI). Total body BMD measurements were normalized for peak values in young white males (T scores) and compared with the calculated T scores in normal age-matched boys.13

Prior to treatment, and every 6 months thereafter, patients were evaluated by a cardiologist with electrocardiograms and echocardiograms, and by an ophthalmologist who tested for the presence of cataracts. Parents were instructed to provide their children with a diet low in sodium and simple sugars.

Data Analysis. The first motor ability lost during the course of DMD is arising from the floor.36 Accordingly, prolongation of the ability to get up from the floor was chosen as the primary measure of treat-
ment efficacy. Secondary outcome measures were arm megascore (sum of the strength of elbow flexion and grip), leg megascore (sum of knee flexion and extension strength), and timed tests (walking 10 m and climbing stairs). The differences in the two groups were compared by Pearson’s chi-square test. All continuous data were expressed in terms of mean and standard deviation (SD). A nonparametric Mann–Whitney rank test calculated by the Monte Carlo method (for small samples) was performed to check the Mann–Whitney results. For all tests, $P < 0.05$ was considered statistically significant. Data were analyzed using the Statistical Package for the Social Sciences software version 9.0 (SPSS, Inc., Chicago, IL).

RESULTS

Five parents chose the prednisone group for their children and three opted for the control group. Age did not differ (Table 1) between the treated and control groups, either at the start (3.5 ± 0.7 vs. 3.5 ± 0.4 years) or at follow-up (8.3 ± 0.8 vs. 8.2 ± 0.9 years). During the treatment period there were no dropouts or changes of group. The duration of prednisone treatment ranged from 47 to 63 months. After a mean 55-month treatment, the patients in the prednisone group were still able to arise from the floor at an average age of 8.3 years, whereas two of the three in the control group had lost this ability. Pearson’s chi-square test showed that the difference between the two groups was significant ($P = 0.035$). Nevertheless, all patients in the two groups remained able to walk and climb stairs at a mean age of 8.2 years. Performances on timed tests (steps and walk of 10 m) did not differ between the two groups. Respiratory function measured as FVC was above 90% in all patients. Mean isometric muscle strength was higher in the treated than in the control group (88.6 ± 21.4 N vs. 55.3 ± 19.6 N in the arm; 159.8 ± 64.6 N vs. 86.0 ± 34.5 N in the leg), but the differences were significant only for the leg megascore with the Moses test.

Side Effects. During the trial period, growth rate declined significantly in prednisone-treated patients ($P = 0.036$). The difference between the height SDS at follow-up and at the start of treatment time was on average $-0.80$ (range $-1.24$ to $-0.27$) in prednisone-treated patients and $+0.02$ (range $-0.13$ to $+0.38$) in untreated patients.

At the start of treatment, all patients were of normal weight except for one in the control group who was underweight by 24%. At follow-up, BMI SDS was on average $+2.5$ (SD = 2.21) in the steroid group and $+1.25$ (SD = 2.27) in the control group (nonsignificant). Body weight excess was 29.7% (range $+13.3$ to $+38.1$%) in the steroid group and 12.9% (range $-2.1$ to $+34$%) in the control group (nonsignificant). Blood count, biochemical values, and hormonal values remained within normal limits. Bone age was progressively retarded in four prednisone-treated and in three control patients. Total body BMD $T$ scores of the children with DMD were significantly lower than in normal age-matched boys ($-4.48 \pm 0.33$ vs. $-3.11 \pm 1.12$), but there was no significant difference between patients in the steroid and control groups ($-4.32 \pm 0.20$ vs. $-4.89 \pm 0.23$).

During follow-up, cushingoid appearance, hirsutism, or acne was not observed. Behavioral changes, consisting of irritability and hyperactivity, were only slightly more common among treated patients and did not require additional complementary medica-

### Table 1. Study data.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age at Entry (Years)</th>
<th>Age at Follow-Up (Years)</th>
<th>Duration of Treatment (Months)</th>
<th>Waltron’s Scale</th>
<th>Rising Time (s)</th>
<th>Steps Time (s)</th>
<th>10-m Time (s)</th>
<th>FVC (ml) (% of Predicted)</th>
<th>Arm Megascore (N)</th>
<th>Leg Megascore (N)</th>
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FVC, forced vital capacity; N, Newton; arm megascore, summed strength of elbow flexion and grip; leg megascore, sum of knee flexion and extension strength.
tion. Only one patient had some difficulty in sleeping and he was treated with niaprazine. Cardiac examination was normal in all patients and there was no evidence of cardiomyopathy on the echocardiogram. Cataracts were not detected.

DISCUSSION

This pilot, open parallel-group, double-consent study showed a beneficial effect of early prednisone treatment on boys with DMD by prolonging the ability of rising from the floor. It also showed that alternate-day, low-dose prednisone is effective in long-term treatment and it is accompanied by fewer side effects. Some 600 published DMD patients have received various steroid treatments, most with beneficial effects, but only 4 of these patients were under the age of 4 years at the start of therapy. A previous identical alternate-dose schedule applied for only 6 months gave variable results. Accordingly, before this study, it was not possible to infer the usefulness of early administration of prednisone.

Children receiving prednisone had a mean isometric muscle strength 60% higher in the arms and 85% higher in the legs compared with untreated children, but only the latter reached significance. Although the timed test data did not reach statistical significance, they paralleled the improved leg strength, in keeping with the beneficial effect of the steroid treatment.

There is major concern about long-term steroid treatment, particularly in young children, because of its well-known adverse effects. We observed significant growth retardation during the treatment period in the steroid group. DMD patients are known to be significantly shorter than the normal population but do not show growth hormone deficiency. Moreover, it seems that the short stature is unlikely to be the result of muscular weakness. It is also known that DMD patients on long-term steroid treatment show less growth than controls. We informed the parents that smaller boys with DMD might have a slower growth rate, 29,39 and begin to develop while they are still ambulant.

Cataracts were not observed in our patients on prednisone, but are a frequent complication associated with steroid treatment.

An evidence-based review of studies of steroids in DMD showed that, until a definitive treatment is available, the use of deflazacort and prednisone with judicious dietary control and close clinical monitoring for side effects is the best intervention for preserving function. We used prednisone rather than deflazacort, because, at the time of planning for our study, the efficacy of deflazacort had not been proven. In addition, contrasting views exist regarding the effects of deflazacort on growth rate, weight increase, and bone loss. Our long-term, parallel-group, open study of low-dose, alternate-day prednisone showed that this approach was effective in maintaining the ability to rise from the floor in a cohort of DMD patients started on treatment before the age of 4 years. Side effects did not differ from those observed in DMD patients started on treatment later in the disease. As long-term steroid treatment is effective in prolonging function but not in recovering lost function, its early use seems appropriate.

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REFERENCES


