

ABSTRACT: We randomized 18 Duchenne muscular dystrophy (DMD) boys whose age ranged from 5.2 to 14.6 years (mean, 7.3 years) for treatment with either deflazacort (0.9 mg/kg/day) or prednisone (0.75 mg/kg/day) on the basis of age and functional score at the onset of treatment. We followed the patients every 3 months for 1 year, evaluating four limb muscles with the Medical Research Council scale and performance of four functions (walking, climbing stairs, Gowers' maneuver, and rising from a chair). Side effects were monitored by a questionnaire and by routine blood examination, and weight and height were recorded at each visit. At 12 months, the effect of both steroids was examined by comparing the status of the treated patients with another group of untreated DMD patients that served as natural history control. The two steroids were equally effective in improving motor function and functional performances. At 9 months, the average weight increase with respect to baseline value was 5% (2 kg) in the deflazacort group but 18% in the prednisone group ($P < 0.005$), and the change remained significant after 12 months ($P < 0.05$). Other minor but nonsignificant side effects were observed. Steroid treatment with deflazacort appears to cause fewer side effects than with prednisone, particularly weight gain, which could be important to maximize motor performances.

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A MULTICENTER, DOUBLE-BLIND, RANDOMIZED TRIAL OF DEFLAZACORT VERSUS PREDNISONE IN DUCHENNE MUSCULAR DYSTROPHY

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Steroids have demonstrated efficacy in slowing the progression of Duchenne muscular dystrophy (DMD) and in delaying the loss of independent ambulation.^{4,6,8–10} In previous studies, different steroids and various dosing regimens have been used in the hope of obtaining maximal efficacy with fewer side effects. Many uncertainties remain about the best steroid regimen and the type of steroid to be used, because comparative trials with these targets have not yet been done. Two controlled double-blind trials of deflazacort versus placebo^{2,8,14} showed that de-

flazacort might have fewer side effects than prednisone, but no direct comparison of these two drugs was reported. To clarify this issue, we have carried out a double-blind, randomized, multicenter trial with deflazacort (0.9 mg/kg/day) versus prednisone (0.75 mg/kg/day) and now present the results after 1 year of treatment.

MATERIALS AND METHODS

Patients. Duchenne muscular dystrophy children from two neuromuscular centers (Pavia and Padua) were selected to participate in the trial. Inclusion criteria were: diagnosis of DMD confirmed by dystrophin immunohistochemistry, age over 5 years, preserved ability to ambulate independently, and no previous steroid therapy. No patient had any recognized contraindication to steroid therapy. With these criteria, 18 DMD patients were randomized to treat-

Abbreviations: DMD, Duchenne muscular dystrophy; MRC, Medical Research Council

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ment with deflazacort (0.9 mg/kg/day) or an equivalent dose of prednisone (0.75 mg/kg/day). Seven ambulant DMD patients served as natural history controls. Drug equivalence was calculated on the basis of seven large trials involving 160 patients, where it was estimated that deflazacort is 25% less potent than prednisone, with a potency ratio of 1:1.3.¹³ Our trial was approved by the ethical committees of the two University Centers, and parents gave written informed consent. The two groups were randomized and stratified on the basis of age and disease severity to obtain two clinically homogeneous groups. Thus, at the beginning of treatment the two groups were similar in mean age and functional parameters. The patients with deflazacort had a mean age of 8.6 years (range, 5.3–14.6 years), whereas the patients on prednisone had a mean age of 7.5 years (range, 5.1–10 years). Natural history controls had a mean age of 6.9 years (range, 6–8 years).

To gain familiarity with functional exercises, all patients were seen twice before the beginning of the trial. Neither the treating physician nor the patient's family knew whether a child was on prednisone or deflazacort. In one center (Pavia) all assessments of patients were filmed, after informed consent, to ensure that functional tests were performed in the same manner at the two centers. One patient, who was treated with both drugs (first 6 months with prednisone and next 6 months with deflazacort), was not included in the evaluation of results.

Muscle strength was evaluated by the Medical Research Council (MRC) scale in four muscles, two in the right upper limb (deltoid and triceps muscles) and two in the right lower limb (ileopsoas and quadriceps femoris muscles); the summed MRC score was used in comparing the two groups in our statistical analysis.

The functional tests evaluated according to our graded protocol³ were gait (walk for 10 m), rising from a chair and from the floor, and climbing four steps. In our protocol, a lower score indicates a better functional performance. A sum of the grades in the functional scores was calculated. We also measured the time required to perform each functional exercise.

At the beginning of the trial and every 3 months thereafter, we performed biochemical and neurological screening tests (serum creatine kinase, glucose, electrolytes, hematocrit, and complete blood count), and monitored height, body weight, and blood pressure of the patients in order to detect steroid side effects. The occurrence of cushingoid appearance, acne, and hirsutism were evaluated by

clinical examination. Parents were asked to report behavioral changes, insomnia, anorexia, increased appetite, or gastrointestinal problems. An x-ray of the left hand for bone age and an eye examination for cataract were performed at the beginning and after 1 year of steroid treatment. We suggested a diet to both groups to limit weight gain.

Statistical Analysis. We evaluated the differences in MRC and functional score at 3, 6, 9, and 12 months with respect to baseline. Statistical significance was checked using the Mann–Whitney test. The MRC and functional scores are not normally distributed and so we applied a nonparametric analysis. The Bonferroni correction was applied to the results. Change in body weight was evaluated with the Student's *t*-test applied to percentage increase with respect to the initial weight.

RESULTS

Drug Comparison. After 1 year, no significant differences were found between the two treatment groups in either MRC score or functional score. The two groups were quite similar both in the MRC score (Fig. 1A) and in functional score (Fig. 1B) at 3, 6, and 9 months. We compared the data for individual tests in the functional score and found no significant difference between the two groups. During follow-up, there was only one drop-out patient in the prednisone group, with loss of independent ambulation. In the functional scores there was an apparent improvement in the prednisone group scores, between the 9th and 12th month. This was due to the drop-out patient who had had more severe scores. The absolute values of scores appeared better in the deflazacort group, but the difference did not reach statistical significance. This type of response could be related to a slightly less severe initial baseline values for the deflazacort group. Altogether, no significant difference was found in the effect of the two drugs on DMD patients. Historical DMD controls with a mean age of 6.9 years (range, 6–8 years) showed a steady and progressive downhill course during a follow-up of 1 year.

Side Effects. The average increase from the initial weight was 2.17 kg in the deflazacort group versus 5.08 kg in the prednisone group at 12 months. The mean weight increase, expressed as percentage of the initial weight, was significantly different at 6 months ($P < 0.05$), and the difference remained statistically significant at 9 and 12 months. After 1 year, the mean weight increase was 9% in the deflazacort group and 21.3% in the prednisone group. Only one

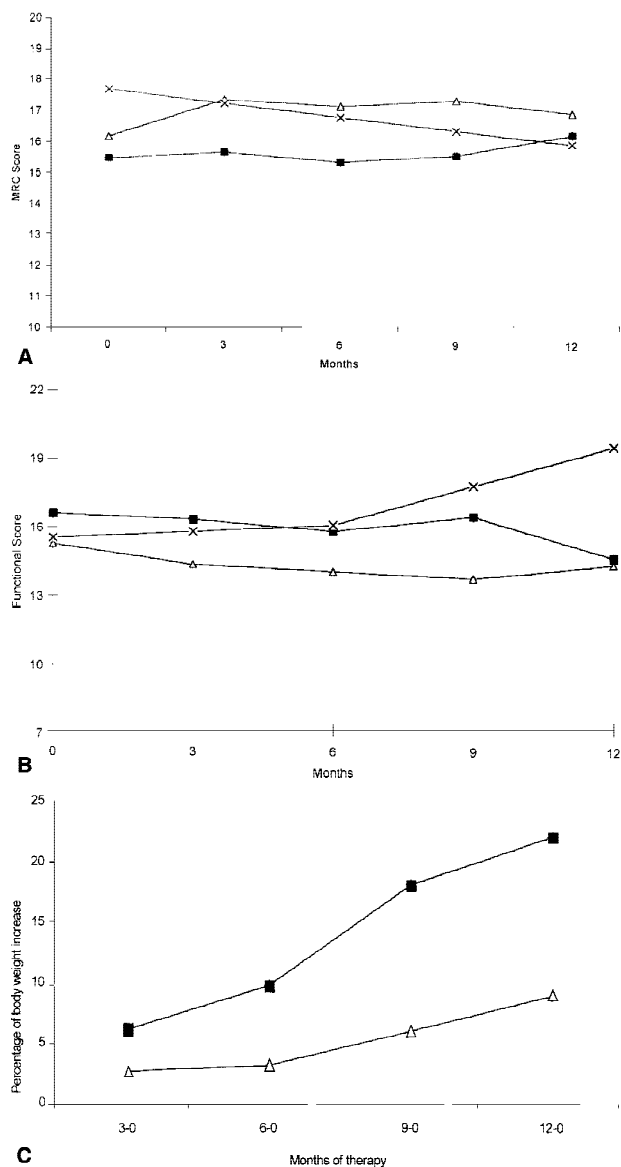


FIGURE 1. (A) Medical Research Council score in deflazacort- and prednisone-treated groups shows stabilization of strength after an initial, slight improvement. Natural history controls show a continuous decline of strength. **(B)** Functional score in deflazacort- and prednisone-treated groups shows a slight improvement in both groups at the beginning of therapy, whereas the natural history group tends to increase in grade and worsen progressively. **(C)** Percentage of body weight increase in deflazacort- and prednisone-treated groups. A less significant increase in weight was found in patients treated with deflazacort after 6 months. Solid square (■) indicates prednisone group, open triangle (△) indicates deflazacort group, and cross (x) indicates natural history group.

patient in the deflazacort group had an increase in body weight of over 20% with respect to baseline, but four patients in the prednisone group had an increase in body weight of over 20% (Fig. 1C). During 1 year of treatment, bone age was similar in the two

groups. After 4 months of therapy, one patient in the deflazacort group reported a traumatic bone fracture. Eye examination by slit lamp revealed a slight cataract in two patients in the deflazacort group and in one in the prednisone group.

No significant change in the laboratory parameters, including serum creatine kinase, occurred in the two groups. Other side effects—such as behavioral changes, increased appetite, and cushingoid appearance—were slight and equally distributed in the two groups, as shown in Table 1. Treatment with antacids for complaints of gastrointestinal pain was provided in 11% of the children in the deflazacort group and 12% in the prednisone group, with complete resolution of pain. Monitoring for other possible side effects revealed no case of hypertension, ankle edema, acne, insomnia, or anorexia.

DISCUSSION

Although the number of patients in each group is small, our trial is the first one that directly compares in a double-blind, randomized way the effect of two types of steroids in DMD. We found that both deflazacort and prednisone are equally effective in slowing disease progression. Thus, no difference was present in the MRC score or functional scores after 1 year of therapy. It is still possible, however, that a type II error exists because of the small number of patients in each group, but this is unlikely to affect our conclusions, which accord with the experience accumulated previously in the use of both drugs.^{2,4,7}

We observed a clear improvement in the first 6 months of therapy among the treated children compared with historical controls,¹⁻³ followed by a stabilization of disease course. In a previous study,² we observed that the placebo group showed a clear decline in MRC index and in a number of functional parameters between 6 and 12 months compared with the deflazacort group.

Lanza et al.¹¹ observed different effects of various corticosteroids on cytokine production, suggesting that different glucocorticoids differ in their binding to the steroid receptor, in their affinity properties, and in their tissue-specific metabolism and interaction with transcription factors.

Because the two types of steroids that we studied are similar in their clinical efficacy, other considerations are important when deciding which one should be used to treat a DMD boy.⁷ The incidence and type of side effects are important in this regard. In our trial, deflazacort appears to cause less increase in body weight. It is unlikely that the difference in weight results from different physical activity, because the children had similar functional abilities.

Table 1. Incidence of side effects in the two groups after 6 and 12 months of treatment.

Side effects	Deflazacort, 6 mo, n (%)	Prednisone, 6 mo, n (%)	Deflazacort, 1 yr, n (%)	Prednisone, 1 yr, n (%)
Cushingoid appearance	2 (22%)	3 (37%)	5 (55%)	4 (50%)
Appetite increase	2 (22%)	6 (75%)	3 (33%)	6 (75%)
Increase in body weight (>20% of baseline)	—	—	1 (11%)	4 (50%)
Behavioral changes	4 (44%)	4 (50%)	6 (66%)	5 (62%)
Gastric symptoms	1 (11%)	2 (25%)	1 (11%)	1 (12%)
Hirsutism	5 (55%)	4 (50%)	5 (55%)	3 (37%)

Other studies on the differential effect of deflazacort and prednisone on bone mass and body composition have been done in kidney transplant patients.¹² The results suggested that using deflazacort instead of prednisone is associated with decreased loss of total skeleton and lumbar spine bone mineral density but does not alter bone loss at the upper femur. Deflazacort also helped to prevent fat accumulation. In a trial of deflazacort versus prednisone conducted in juvenile chronic arthritis, the weight loss found in the first year in the deflazacort group was regained in the following 12 months.⁵ It will therefore be important to follow our patients on a long-term basis to evaluate further changes in body weight and to study their growth. The increase in body weight could be particularly important in nonambulant DMD patients, because it may reduce the benefit of steroids on motor performances. The increased weight in nonambulant children on a long-term basis could also increase spinal deformity. It is therefore important to evaluate benefit versus side effects in a long-term follow-up study with particular regard to bone formation and growth.

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