

A Multicenter Double-Blind Randomized Trial of Deflazacort Versus Prednisone in Duchenne Muscular Dystrophy: Analysis after 2 Years

Marco D. Bonifati, Giampietro Ruzza, Piero Bonometto, Angela Berardinelli⁽¹⁾, Kseniya Gorni⁽¹⁾, Simona Orcesi⁽¹⁾, Giovanni Lanzi⁽¹⁾, Mario Ermani, and Corrado Angelini

Neuromuscular Center, Department of Neurology, University of Padova, Padova, and (1) Department of Child Neurology, Istituto Mondino, University of Pavia, Pavia, Italy

Abstract

We have conducted a double-blind, randomized, multicentric trial in 18 Duchenne muscular dystrophy (DMD) boys, whose age ranged from 5.2 to 14.6 years (mean 7.3 yrs) for treatment with either deflazacort (0.9 mg/kg/day) or prednisone (0.75 mg/kg/day). To reduce side effects after one year the treatment schedule was switched to an alternate day regimen. The two groups were randomized and stratified on the basis of age and functional score at the onset of treatment.

We followed the patients every 3 months in the first year and then every four months, evaluating MRC scale in four limb muscles, two in the right upper limb (deltoid and triceps) and two in the right lower limb (ileopsoas and quadriceps femoris) and performance of four functions (walking for 10 meters, climbing stairs, Gowers' manoeuvre, and rising from a chair). We evaluated the differences in MRC and functional score with respect to baseline. Statistical significance was calculated by the Mann-Whitney test. Side effects were monitored by a questionnaire and by routine blood examination (serum creatine kinase, glucose, ions, hematocrit and complete blood count) and weight and height were recorded at each visit. Change in body weight was evaluated with the student t-test. After 24 months there were 2 drop out patients in the deflazacort group and 3 in the prednisone group for loss of independent ambulation. The two steroids were equally effective improving motor function and functional performances in the first 6 months and then we observed a slow down in the course of the disease.

At 9 months, the average weight increase respect to baseline value was 5% (2 Kg) in the deflazacort group and 18% in the prednisone group ($p < 0.005$) and after 24 months it was 19% in the deflazacort group and 41% in the prednisone group. Only 3 patients on deflazacort had an increase in body weight that exceeded 20% with respect to baseline, but all the remaining patients in the prednisone group had an increase in body weight of over 20%.

Two fractures occurred in the deflazacort group. Bone formation and growth evaluated with X-ray of the left hand for bone age did not appear different in the two groups. Eye examination revealed a slight cataract in 3 patients in the deflazacort group and in 1 in the prednisone group. Other minor and slight side effects such as behavioural changes, increased appetite and cushingoid appearance were observed in both groups.

Steroid treatment with deflazacort appears to cause less side effects than prednisone, particularly on weight gain, which could be important to maximize motor performances and to avoid long term complications such as spinal deformity and respiratory fatigue.

Key words: Deflazacort, Prednisone, Duchenne Dystrophy, trial.

Basic Appl Myol 10 (4): 171-175, 2000

A multicenter double-blind randomized trial of deflazacort versus prednisone in Duchenne muscular dystrophy

Duchenne muscular dystrophy is a progressive muscle disease with fatal course characterised by the absence of dystrophin, a subsarcolemmal protein. The boys affected by the disease usually became wheelchair-bound at about 10 years of age.

Actually no resolutive therapy exists for the disease. Awaiting gene therapy, steroids have demonstrated good efficacy in slowing the progression of the disease and delay the loss of deambulation in many studies [1-5]. In previous studies different steroids with different regimens have been used with the aim to obtain the maximal efficacy with less side effects. However many doubts remain about when to begin the therapy, the best steroid regimen and the type of steroid to use lacking clinical trials with these targets as primary end-points [19]. Two trials [6-7] stated that deflazacort has fewer side effects than prednisone. Particularly deflazacort has been shown a sparing bone loss action in children with other disease [8].

To answer to the question of the best steroid to use we have carried out a double-blind, randomized, multicentric trial with deflazacort 0,9 mg/Kg/die versus prednisone 0,75 mg/Kg/die. We present here results after two years of treatment. In the design of the trial after one year the treatment has been switched to an alternate dose regimen, maintaining the same dosage, to reduce side effects.

Materials and Methods

Patients

The trial was approved by the ethical committee of University of Padua and that of the Lombardy region and the parents gave written informed consent. 18 deambulant patients with Duchenne muscular dystrophy confirmed by dystrophin immunohistochemistry from two Italian neuromuscular centers (Pavia and Padua) were randomized in two groups with equivalent dosage of deflazacort and prednisone (0,9 mg/Kg/die versus 0,75 mg/Kg/die). The two groups were randomized on the basis of age and disease severity, so no differences were present at the beginning of treatment.

The patients in Deflazacort had a mean age of 8,6 years (range 5,3-14,6) while the patients in Prednisone had a mean age of 7,5 years (range 5,1-10).

All patients underwent two visits before the beginning of the trial to assure complete compliance with the functional tests and a monitor controlled the correct application of the protocol in the two centers. In the second center (Pavia) the patients were filmed after informed consent, to permit a double blind check of the results. One patient was treated with the two drugs: first 6 months with prednisone and after with deflazacort. This patient has not been considered in the evaluation of results.

We have evaluated strength and functional ability every three months in the first year and then every 4 months. Strength was evaluated with MRC scale in four muscles, two in the upper limbs (deltoid and triceps) and two in the lower ones (ileo-psoas and femoral quadriceps) and with four functional tests.

The functional tests evaluated were gait (walking for ten meters), rising from a chair and from the floor, climbing four steps and functionality of upper limbs.

In the first four tests we measured the time employed to perform the exercises so it was possible to calculate GSCG compound score. GSCG is a mathematical formula that makes more sensitive the score of the functional tests [15].

At the beginning of the trial and during the study we monitored blood exams (CPK, glucose, ions and full blood count), height, body weight and blood pressure to check steroids side effects. Cushingoid appearance and hirsutism were evaluated and we asked the parents to refer about behavioral changes or gastrointestinal problems. An X-ray of the left hand for bone age and an eye exam for cataract were performed at the start and after one year. To reduce weight gain we suggested a diet to both groups.

Statistical analysis

We evaluated the differences in MRC, functional and GSCG score at 6, 12, 18 and 24 months with respect to baseline. Statistical significance was checked by the Mann-Whitney test. The MRC, functional and GSCG scores are not normally distributed and so we applied a nonparametric analysis. The Bonferroni correction was applied to the results. Student t-test has been applied to percentage increase with respect to the initial weight.

Results

After two years no significant differences were found between the two groups in the MRC score, functional score and GSCG compound score (Fig 1). The two groups were quite similar at any stage of the study. The curves are parallel and do not differ between the two drugs. No statistically difference were found analysing data for single test of functional score and GSCG score. During the follow up there were three drop-out cases in the prednisone group and two in the deflazacort group for loss of deambulation. To avoid the bias related to the drop-outs of the more severe patients we have maintained these patients in the calculations with the last score obtained. In fact the score is set up primarily for ambulant patients. The slope of different scores appears better in the Deflazacort group but the difference doesn't reach statistical significance. This type of response could be related to a slight less severe degree of compromise in the initial baseline values for the deflazacort group.

A multicenter double-blind randomized trial of deflazacort versus prednisone in Duchenne muscular dystrophy

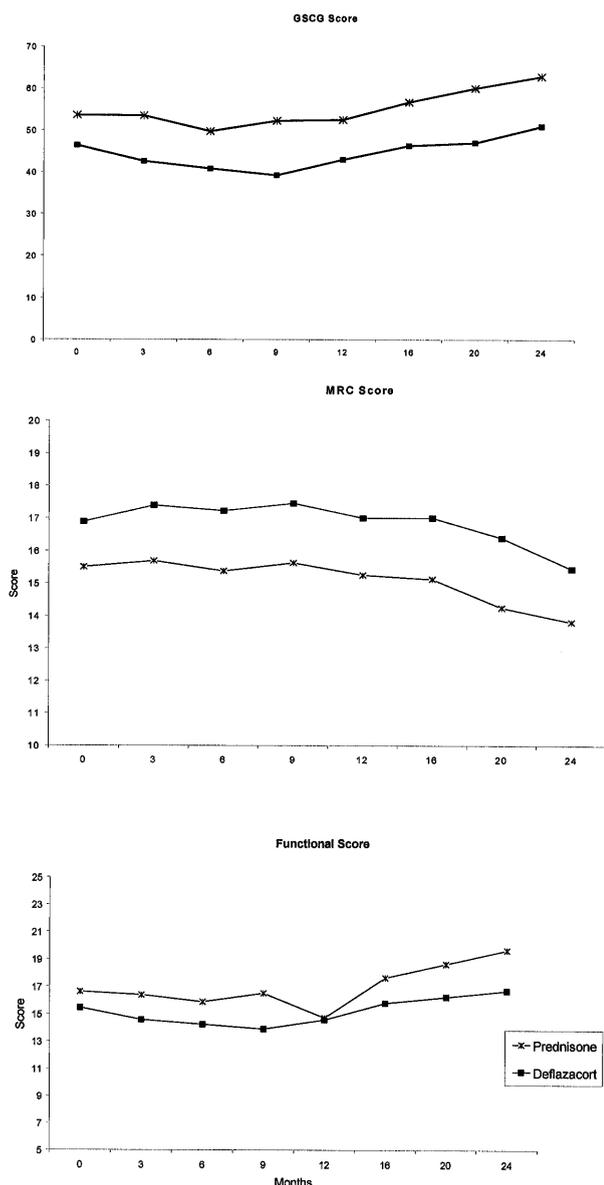


Figure 1. Course of GSCG score, muscle strength measured by MRC scale and functional score, over 2 years, in 17 DMD patients.

The results about the increase in body weight are interesting. The average increment from the initial weight was 4,6 Kg in the deflazacort group versus 8,7 Kg in the prednisone one at 24 months. The difference between the two groups became statistical significant after 9

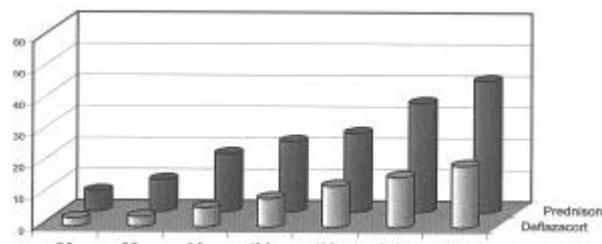


Figure 2. Weight percentage increase respect baseline shows greater increase in the prednisone group

months ($p < 0,05$) (Tab 1).

After two years only 4 patients in deflazacort group had an increase in body weight over 20% respect baseline (maximum 34%) against all patients in prednisone group (maximum 48%) (Fig. 2).

Eye examination revealed a slight cataract in 3 patients in the deflazacort group and in 1 in the prednisone group. Other minor slight side effects such as behavioural changes, increased appetite and cushingoid appearance were observed in both groups.

No change in laboratory parameters including creatine phosphokinase was observed in the two groups. Other side effects as behavioral changes, increased appetite and cushingoid appearance were rare and randomly distributed in the two groups as it is shown in table two. The children were treated with antiacids only if they complained about some gastrointestinal pain. This occurred in 33% children in deflazacort group and in 62,5% in prednisone group with complete regression after the beginning of the therapy. Two fractures occurred in the deflazacort group but no differences in bone age has been found in the two groups.

Discussion

Our results answer to an important question in the steroid treatment of Duchenne muscular dystrophy in fact both deflazacort and prednisone appear to be equally effective in slowing the progression of the disease. No difference is present both in the force measured with MRC score and functional ability. In the first trial with steroids in DMD Siegel et al. compared 7 DMD patients treated with prednisolone (5 mg/Kg on alternate days) with 7 age-matched pair-mates in placebo. The authors with a pessimistic point of view defined the results as 'transient and minimal slowing of the disease

Table 1. Mann-Whitney test on weight percentage difference respect baseline value.

| Months | Deflazacort Mean | Prednisone Mean | Deflazacort SD. | Prednisone SD. | p-level |
|--------|------------------|-----------------|-----------------|----------------|---------|
| 0 | 25 | 22,3 | 9,26 | 5,63 | |
| 6 | 25,7 | 24,5 | 9,37 | 6,61 | .020928 |
| 12 | 27,1 | 27,1 | 9,69 | 7,93 | .016150 |
| 18 | 28,7 | 30,5 | 9,86 | 9,38 | .00033 |
| 24 | 29,6 | 29,3 | 10,1 | 6,43 | .00165 |

A multicenter double-blind randomized trial of deflazacort versus prednisone in Duchenne muscular dystrophy

process in several patients' but after two years six of the seven patients in the prednisolone group were ambulant against only two in the controls.

From that study many others followed and more than 200 patients have been treated and many double blind, randomized, controlled trials have been performed [5, 7, 9, 20, 21, 22]. All these trials showed significant benefit of steroid treatment with a marked initial improvement and a slowing in the progression of the disease.

This is the first trial that compares in a double blind, randomized fashion two types of corticosteroids. As in previous trial we observed a clear improvement in the first six months of therapy in all followed by a stabilization or slower decline that become more evident in the second year.

Steroids have been demonstrated to be effective in the treatment of Duchenne muscular dystrophy in many trials. Some mechanisms of action have been supposed to be important in the steroid therapeutic effect:

1. an anabolic effect of the steroids on the muscle has been demonstrated in vitro with low dose of drug while with higher dosage a catabolic effect probably occurs. An increased urinary creatinine excretion has been found in Mendell's trial suggesting an increase in the total muscle mass [9]. On this basis a pilot study with oxandrolone has been performed by Fenichel et al. [12] in ten DMD boys treated for 3 months. An increase in muscle strength has been demonstrated but the effect of this anabolic steroid in a long term treatment are still unknown.
2. an immunosuppressant action reducing the number of cytotoxic lymphocytes [13]. In fact cyclosporine resulted effective in a months trial [10]. However this effect doesn't appear to be the main one since a subsequent trial with azathioprine resulted ineffective in improving strength in Duchenne muscular dystrophy [11].
3. an antifibrotic action slowing the substitution of the muscle with fibrous-adipose tissue avoiding muscle 'cirrhosis' and allowing the regeneration of the muscle to proceed in a correct way.
4. a specific increase in some important membrane cell proteins like dystrophin and utrophin [14, 17, 18]

On the other side different glucocorticoid compounds could have different effects on muscle since they differ in their binding to the steroid receptor, in their tissue affinity and metabolism.

Recently deflazacort but not prednisone has been demonstrated to improve muscle repair and fibre growth in the mdx dystrophic mouse through an effect on promotion of myogenesis [16]. Deflazacort could have its specific effect regulating muscle precursor cells cycling or fusion

Since the two types of steroid are not different in the clinical improvement other considerations are important

in the decision of how to treat a boy with Duchenne dystrophy. The incidence and types of side effects remain the main factor we should consider in the decision.

In our trial, for the first time, two types of steroid are compared in a randomized, double blind fashion. After two years we have a similar trend of the two types of steroids in clinical efficacy. Deflazacort appears to reduce the increase in body weight. The difference in body weight, slight in the first year, becomes more evident in the second year. The increase in body weight could be particularly important in Duchenne muscular dystrophy since an increase in body weight could reduce the effects of steroid in motor performances and weight gain might cause a major stress on muscle fibers that results in increase in muscle necrosis. Overweight could increase spine deformity when patients became wheel-chair-bound. After two years there was a slight major prevalence of cataracts in the deflazacort group. Similar data from a multicenter deflazacort versus prednisone, randomised trial were seen by Reitter et al. (Personal communication) and relevance of these data were discussed at the 75th Workshop of the European Neuromuscular Center on the treatment of Duchenne Muscular Dystrophy.

Aknowledgments

This study was supported by Telethon grant 916C, MURST 9906193744001 and CNR grant 9703985CTO4.

Address correspondence to:

Corrado Angelini, Neuromuscular Center, Department of Neurology, via Giustiniani 5, University of Padova, 35121 Padova, tel. 0039 049 8213610, fax 0039 049 8751770, Email cmusc@ux1.unipd.it.

References

- [1]Brooke MH, Fenichel GM, Griggs RG, Mendell JR, Moxley RT, Miller JP, Kaiser KK, Florence JM, Pandya S, Signore L, King W, Robison J, Head RA, Province MA, Seyfried W, Mendell S: Clinical investigation of Duchenne muscular dystrophy. Interesting results in a trial of Prednisone. *Arch Neurol* 1987; 44: 812-817.
- [2]De Silva S, Drachman DB, Mellits D, Kuncel RW: Prednisone treatment in Duchenne muscular dystrophy. Long-term benefit. *Arch Neurol* 1987; 44: 818-822.
- [3]Dubrovsky AL, Mesa L, Corderi J, Marco P, Flores D: Deflazacort in Duchenne dystrophy dose-dependent effect. *Neurology* 1992; 42: 227.
- [4]Fenichel GM, Florence JM, Pestronk A, Mendell JR, Moxley RT, Griggs RG, Brooke MH, Miller JP, Robison J, King W, Signore L, Pandya S, Schierbecker J, Wilson B: Long-term benefit from prednisone ther-

A multicenter double-blind randomized trial of deflazacort versus prednisone in Duchenne muscular dystrophy

- apy in Duchenne muscular dystrophy. *Neurology* 1991; 41: 1874-1877.
- [5] Fenichel GM, Mendell JR, Moxley RT, Griggs RG, Brooke MH, Miller JP, Pestronk A, Robison J, King W, Signore L, Pandya S, Florence JM, Schierbecker J, Wilson B: A comparison of daily and alternate-day prednisone therapy in the treatment of Duchenne muscular dystrophy. *Arch Neurol* 1991; 48: 575-579.
- [6] Angelini C, Pegoraro E, Perini F, Turella E, Intino MT, Pini A, Ottolini A, Costa C: A trial with a new steroid in Duchenne muscular dystrophy, in Angelini C, Danieli GA and Fontanari D (eds): *Muscular dystrophy research*. New York, Elsevier, 1991, pp 173-179.
- [7] Mesa LE, Dubrovsky AL, Corderi J, Marco P, Flores D: Steroids in Duchenne dystrophy Deflazacort trial. *Neuromuscul Disord* 1991; 4: 261-266.
- [8] Loftus J, Allen R, Hesp R, David J, Reid DM, Wright DJ, Green JR, Reese J, Ansell BM, Woo PM: Randomized double-blind trial of deflazacort versus prednisone in juvenile chronic (or rheumatoid) arthritis: a relatively bone sparing effect of deflazacort. *Pediatrics* 1991; 88: 428-436.
- [9] Mendell JR, Moxley RT, Griggs RG, Brooke MH, Fenichel GM, Miller JP, King W, Signore L, Pandya S, Florence JM, Schierbecker J, Robison J, Kaiser KK, Mandell S, Arfken C, Gilder B: Randomized, double blind six-month trial of Prednisone in Duchenne's muscular dystrophy. *N Engl J Med* 1989; 320: 1592-1597.
- [10] Sharma K, Mynhier MA, Miller RG: Cyclosporine increases muscular force generation in Duchenne muscular dystrophy. *Neurology* 1993; 42: 527-532.
- [11] Kissel JT, Lynn J, Rammdan K, Griggs RC, Moxley RT, Brooke MH, Cwick V, Mendell JR: Mononuclear cell analysis of muscle biopsies in azathioprine treated Duchenne dystrophy. *Neurology* 1992; 42 (suppl 3): 227.
- [12] Fenichel G, Pestronk A, Florence JM, Robison J, Hemelt V: A beneficial effect of oxandrolone in the treatment of Duchenne muscular dystrophy: a pilot study. *Neurology* 1997; 48: 1225-1226.
- [13] Kissel JT, Burrow KL, Rammohan KW, Mendell JR, CIDD Study Group: Mononuclear cell analysis of muscle biopsies in prednisone-treated and untreated Duchenne muscular dystrophy. *Neurology* 1991; 41: 667-672.
- [14] Hardiman O, Sklar RM, Brown PH: Methylprednisolone selectively affects dystrophin expression in human muscle cultures. *Neurology* 1993; 43: 342-345.
- [15] Knaflitz M, Balstra G, Angelini C, Cadaldini M: Muscle fatigue evaluation in the follow-up of children affected by Duchenne muscular dystrophy *BAM* 1996; 6 (2): 115-123.
- [16] Anderson JE, McIntosh L, Poettcker R: Deflazacort but not prednisone improves both muscle repair and fiber growth in diaphragm and limb muscle in vivo in the MDX dystrophic mouse. *Muscle Nerve* 1996; 19: 1576-1585.
- [17] Sklar RM, Brown RH Jr: Methylprednisolone increases dystrophin levels by inhibiting myotube death during myogenesis of normal human muscle in vitro. *J Neurol Sci* 1991; 101: 73-81.
- [18] Pasquini F, Guerin C, Blake D, Davies K, Karpati G, Holland P: The effects of glucocorticoids on the accumulation of utrophin by cultured normal and dystrophic human skeletal muscle satellite cells. *Neuromuscul Disord* 1995; 5: 105-114.
- [19] Dubrovsky AL, Angelini C, Bonifati DM, Pegoraro E, Mesa L: Steroids in muscular dystrophy: where do we stand? *Neuromuscul Disord* 1998; 8: 380-384.
- [20] Griggs RC, Moxley RT, Mendell JR, Fenichel GM, Brooke MH, Pestronk A, Miller JP: Prednisone in Duchenne dystrophy: a randomized, controlled trial defining the time course and dose response. *Arch Neurol* 1991; 48: 383-388.
- [21] Backman E, Henriksson KG: Low-dose prednisolone treatment in Duchenne and Becker muscular dystrophy. *Neuromuscul Disord* 1995; 5 (3): 233-241.
- [22] Angelini C, Pegoraro E, Turella E, Intino MT, Pini A, Costa C: Deflazacort in Duchenne dystrophy: study of long-term effect. *Muscle Nerve* 1994; 17 (4): 386-391.