benefits observed.

Adverse effects

One has to be cautious in evaluating the adverse effects of glucocorticoid corticosteroid therapy reported in these included studies and extrapolating from them for long-term clinical use. Four of the five included studies used prednisone/prednisolone on a daily dose basis over the short-term six-month period. The longest included study, of two years' duration, (Angelini 1994) used deflazacort 2 mg/per kg on alternate days. The side effects observed during these studies would be much less than in the circumstances where glucocorticoid corticosteroids are used for five years or longer, as may be anticipated in clinical practice. Some of the long-term side effects, especially the effect on bone mineral density, bone fracture incidence, cataracts and growth failure with short stature, cannot be anticipated to have been detected in these short-term studies.

The propensity for excessive weight gain on glucocorticoid corticosteroid treatment was clear. This did not appear to adversely affect strength or function in these short-term studies, except for one participant (in the prednisone 0.3 mg/kg/day group) who at the end of the six months of the Griggs 1991 study refused to continue into another subsequent study of prednisone versus azathioprine (Griggs 1993). Behavioural changes and cushingoid side effects were statistically significant in the glucocorticoid corticosteroid treatment groups but were not considered important enough for treatment to be discontinued in these short-term studies.

Participants treated with prednisone 0.75 mg/kg/day over the six-month period were at significant risk of excessive hair growth. This side effect appears to have been tolerated by the participants and their families and no participants dropped out of the study because of it.

Mendell 1989 and Griggs 1991 demonstrated a trend to develop acne in the prednisone 0.75 mg/kg/ day group during the six months off treatment but this was not statistically significant.

Only one included study (Angelini 1994) reported a pathological fracture (tibia) while on glucocorticoid corticosteroid (deflazacort 2 mg/per kg on alternate days). Duration of treatment prior to the occurrence of fracture and the circumstances of the fracture were not described. One participant in the placebo treatment group in Griggs 1991 dropped out of the study because of an arm fracture (reported in Griggs 1993).

None of the studies assessed bone mineral density by dual energy X-ray absorptiometery (DEXA) scans. This relates to the era during which the studies were carried out and also the short-term nature of the studies. However, in view of the apparent benefit of glucocorticoid corticosteroid therapy in Duchenne muscular dystrophy, the treatment regime is envisaged to be continued in these patients over a decade or longer. In these circumstances, the development of osteoporosis is a major risk and future studies should incorporate systematic DEXA scanning in their protocol for monitoring of side effects.

Prednisone versus deflazacort comparative trials

Of the three randomised controlled trials of deflazacort versus prednisone only one (Bonifati 2000) has been published in detail while the trials of Brooke 1996 (n = 106) and Reitter 1995 (n = 100) have been published only as abstracts or reported in workshop proceedings. Bonifati 2000 is a study with only 18 patients aimed at comparing the adverse effect of prednisone with deflazacort, both being given in a daily dose regime over one year. Power calculations were not presented. The two glucocorticoid corticosteroids had similar benefit on strength and functional tests but there was a statistically significant difference in weight gain, which was more marked in the prednisone treatment group. One out of the nine participants in the deflazacort group, in comparison to four of the nine in the prednisone group gained more than 20% weight over the baseline.

The two unpublished studies (Brooke 1996; Reitter 1995) are of major clinical interest because of the large patient numbers, comparison of prednisone with deflazacort in both the studies and, in addition, comparison of prednisone and deflazacort with a contemporaneous placebo control group in Brooke 1996. The authors of these studies were contacted but data were not available at the time of writing this review.

Campbell 2003 reported similar difficulties in obtaining these data for their systematic review of deflazacort in Duchenne muscular dystrophy. It is our intention in future to supplement this review with comparison of different doses and types of glucocorticoid corticosteroids in Duchenne muscular dystrophy.

Evidence from non-randomised studies

Though non-randomised, these studies listed in Additional Tables, Table 02, still constitute an important body of evidence.

The initial studies

The early open studies to document some benefit of glucocorticoid therapy in Duchenne dystrophy (Drachman 1974; Siegel 1974; Brooke 1987, DeSilva 1987) used prednisone in high doses ranging from 1.5 mg/kg/day to 5 mg/kg on alternate days. The open study by DeSilva et al. (DeSilva 1987) used loss of walking ability as the primary end-point and reported a prolongation of walking by approximately two years. The side effects of steroid treatment in this study were significant and included excessive weight gain in the majority of the patients and also hyperactivity, cataracts, hypertension and stress fractures. These initial studies led to randomised controlled trials (Griggs 1991; Mendell 1989) and further open cohort studies to assess the efficacy and to find the optimal dose regimes to minimize the side effects.

Alternate day prednisone therapy

Fenichel 1991a compared prednisone 1.25 mg/kg on alternate days with prednisone 2.5 mg/kg on alternate day over a six-month period. The study recruited the 103 patients who had just completed the Mendell 1989 randomised study. The placebo control group from the Mendell 1989 was put on prednisone 1.25 mg/kg on alternate days and improved in strength at three months of treatment but showed a decline in strength over the subsequent three months. The participants in Mendell 1989 who were treated with prednisone 0.75 or 1.5 mg/kg/day were changed to 2.5 mg/kg on alternate days for six months in Fenichel 1991a and declined in muscle strength. The authors compared the 1.25 mg/kg alternate day group of Fenichel 1991a with their contemporaneous 2.5 mg/kg alternate day group and also with the placebo control group of the previous Mendell 1989 study and concluded that daily dose prednisone was more effective than the alternate day regime.

Daily prednisone therapy

At the end of the Fenichel 1991a study, 93 of the 103 participants were put on prednisone 0.75 mg/kg/day for two years in an open study, the results of which were published in Fenichel 1991b. There was stabilization of muscle strength, described as average muscle score (previously described as muscle strength score) over a two-year period. Over the two-year period, the prednisone dose had to be decreased because of adverse effects, to as low as 0.15 mg/kg/day. Prednisone 0.65 mg/kg/day was considered to be the minimum effective dose but this could be tolerated by only half of the participants by the end of the study.

Long-term daily prednisone therapy

Pandya 2001 reported the long-term outcome of 30 participants who had received prednisone for a mean period of 10 years. This cohort comprised of a sub-group of participants who were treated with prednisone 0.75 mg/kg/day in the Mendell 1989 and were followed up at the University of Rochester. At the initiation of prednisone, 18 of the 30 participants were ambulant, 13 independently and five walking with long leg braces. At the time of the last visit, one participant was still walking independently at age 18 years, one participant was lost to follow-up and three participants discontinued prednisone because of weight gain. The average age of loss of independent ambulation was 14.5 years. This represents significant improvement in comparison to the previous natural history studies, which reported loss of walking in untreated boys with DMD at mean ages of 8.8 years (Dubowitz 1978), 9.5 years (Gardner-Medwin 1980) and 10.5 years (Allsop 1981). Prednisone dose had to be decreased because of systemic side effects and in this cohort of 30 participants the mean prednisone dose tolerated was 0.35 mg/kg/day.

Daily dose deflazacort studies

Of the non-randomised studies, the most impressive functional results of glucocorticoid corticosteroid therapy in Duchenne muscular dystrophy have been reported by Biggar 2001 and Silversides 2003. Both were retrospective studies from Bloorview MacMillan Children's Centre in Toronto and though not explicitly stated, they represent an overlapping cohort of patients.

Biggar 2001 used deflazacort 0.9 mg/kg/day (starting dose) in 30 boys with Duchenne dystrophy (age 7 to 15 years) over 3.8 years (SD1.5). They compared this group with 24 boys who were followed up at the same clinic contemporaneously but did not take up the option of deflazacort treatment, because of parental choice (the most common reason for choosing not to take deflazacort was fear of side effects). Seven of the 30 boys in the deflazacort group stopped walking at a mean of 12.3 (2.7) years and this contrasted with the non-treated participants, all 24 of whom stopped walking at a mean of 9.8 (1.8) years. The forced vital capacity in the deflazacort-treated group was significantly greater at age 15 years ($p < 0.001$), but the number of participants at 15 years was not reported. None of the deflazacort-treated participants required scoliosis surgery, as compared to 13 of the 24 untreated boys who were over 13.5 years of age at the time of study reporting. Ten of the 30 boys in the deflazacort treatment group developed asymptomatic cataracts. There was also a significant difference in height between the two groups; mean height in the deflazacort-treated group continued along the 3rd centile compared to between the 25th and 50th centiles for the non-treated group.

Silversides 2003 focused on cardiac function as the primary outcome of interest. They reported a cohort of 33 Duchenne patients who underwent echocardiographic evaluation. Twenty-one participants had been on deflazacort for a mean duration of 5.1 years +/- 2.4, and this group was compared with the other 12 who had not accepted the option of deflazacort treatment. The mean age at last follow-up was 14 (2) years for the deflazacort-treated group and 16 (2) years for the non-treated group. This age difference in the two groups was not statistically significant ($p = 0.08$), but the biological significance cannot be discounted. Cardiomyopathy, as indicated by left ventricular ejection fraction of less than 45%, was demonstrated in one of the 21 deflazacort-treated participants, compared to 7 out of 12 non-treated participants ($p = 0.001$). The mean ejection fraction reduction was 33% (70) in the deflazacort group and 21% (8) in the non-treated group ($p = 0.002$). The study also reported a statistically significant preservation of pulmonary function. Mean forced vital capacity was 2.0 (0.4) litres in the deflazacort group and 1.4 (0.5) litres in the non-treated group ($p = 0.001$). Per cent predicted values for forced vital capacity were also significantly better in the deflazacort-treated patients (83% (12) deflazacort group, 41% (19) non treated group; $p < 0.001$). All 12 non-treated boys lost ambulation (mean age 9.8 (1.8) years), and this contrasts with 10 of the 21 boys who stopped walking in the deflazacort group ($p = 0.002$). The dose of deflazacort had to be decreased with duration of treatment to a mean of 0.59 (0.15) mg/kg/day at 18 years. Adverse effects in the deflazacort treated group included asymptomatic cataracts in half of the patients and short stature.

Vertebral fractures with daily dose glucocorticoid regimes

The need for caution with the long-term use of glucocorticoid corticosteroids was highlighted by Bothwell 2003. Twenty-five boys with Duchenne muscular dystrophy were treated with daily glucocorticoids (1 prednisolone, 13 deflazacort, and 11 treated with prednisolone before switching to deflazacort) for a median duration of 4.5 years. The dosage used was 1 mg/kg/day. The authors do not describe whether the dose was reduced over time e.g. in response to excessive weight gain. All boys were prescribed calcium supplements and 22 of the 25 boys were also on Vitamin D. Ten of the 25 boys (40%) sustained vertebral fractures; eight were symptomatic with backache and two had fractures detected on spinal radiographs taken because of low bone mineral density results. The first fracture occurred at 40 months into treatment. Extrapolating from the 10 boys who had sustained a vertebral fracture, Kaplan Meier analysis predicted that 50% of treated boys would have a vertebral fracture by 53.5 months and 75% by 100 months of treatment.

Intermittent glucocorticoid corticosteroid regimes

Dubowitz regime - prednisolone 10 days on 10/20 days off

In order to lessen the adverse effects of long-term glucocorticoid treatment, Dubowitz (Dubowitz 1991) recommended an intermittent regime of prednisolone 0.75 mg/kg/day for the first 10 days of every calendar month (cycles of 10 days on prednisolone treatment, 20 days off treatment). An open study of 32 patients demonstrated that this intermittent regime had a positive influence on strength at six

months followed by a slow decline at 12 and 18 months (Sansome 1993); the weight gain and other side effects were much less than expected with continuous therapy. Subsequently in order to increase the efficacy, the regime was modified to give prednisolone 0.75 mg/kg/day on a 10 days on treatment and 10 days off treatment regime. The long-term tolerability of the intermittent (10 days on treatment, 10 days off) regime of prednisolone was highlighted by the same research group (Dubowitz 2002; Kinali 2002). The four boys reported in these studies were started on prednisolone between four to five years of age and followed up over a period of between 3.75 to over five years. These boys showed "remarkable improvement" (described by authors as gaining the ability to rise from the floor without Gowers' manoeuvre, hop on one or both legs, and run without waddle) and the functional benefit was partly sustained without the evidence of abnormal weight gain, demineralization of bone or other signs of chronic prednisolone toxicity. These studies (Dubowitz 2002, Kinali 2002) though including small numbers also suggested that the beneficial effects of glucocorticoids appear to be greater when treatment is initiated at a younger age, in the early ambulant phase. There are no long-term data reporting prolongation of ambulation with this intermittent regime.

Connolly regime - twice weekly prednisolone (5 mg/kg/dose)

In a further attempt to decrease the long-term adverse effects, Connolly 2002 devised a twice weekly regime of prednisone given every Friday and Saturday (5 mg/kg/dose). Twenty boys (with an average age of eight years) were treated and compared to historical controls. Strength, evaluated with hand held manometer and grip meter, improved over six to 12 months. At least six of the 20 boys developed irritability which led to discontinuation of treatment in two and 25% to 30% dose reduction in four patients. Long-term results for this treatment regime have not been reported.

Controversy in clinical role of glucocorticoid corticosteroids in DMD

The past uncertainty about the long-term use of glucocorticoid treatment in DMD primarily related to the quantum of functional benefit and the attendant adverse effects. The lack of consensus amongst experts is exemplified here. Dubrovsky (Dubrovsky 1998) in his review article on the role of steroids in Duchenne muscular dystrophy, listed 14 published studies and summarized: "The decision to administer steroids is still individual and depends on the wisdom of the experienced physician to use an appropriate dose and schedule, for which purpose we have been trained." In another recent review article, Iannaccone (Iannaccone 2001) concluded: "oral steroids are not recommended for treatment of DMD on a routine basis."

Costs

The oral glucocorticoid corticosteroids, including prednisone/prednisolone and deflazacort are not expensive. In the United Kingdom, the annual cost of prednisolone for a 30 kg boy is estimated at [pounds]120 British pounds sterling and the corresponding figure for deflazacort at the equivalent dosage of 0.9 mg/kg/day is [pounds]450 (BNF 2001). The much bigger costs are those for drug administration and the surveillance required to monitor both the benefits and adverse effects, and these have not been calculated.

The major aim of glucocorticoid corticosteroids in the ambulant phase of Duchenne muscular dystrophy is to prolong the ability to walk. In the natural history course of Duchenne muscular dystrophy, loss of walking ability at the mean age of 9.5 years (range 6 to 13) is followed by development of scoliosis, which is rapidly progressive during the pubertal growth spurt years. This complication requires treatment with bracing and/or surgery. The scoliosis and its treatment have implications for patients' quality of life and involve the anaesthetic hazards and the surgical risks of extensive spine surgery. Data from non-randomised studies suggest that prolongation of ambulation, either with rehabilitation in calipers (Rodillo 1988) or pharmacologically with prednisolone (Tunca 2001) or deflazacort (Biggar 2001), reduces the risk of development and progression of scoliosis. A decrease in incidence of scoliosis and avoidance of scoliosis surgery as a result of glucocorticoid corticosteroid-induced prolongation of walking would reduce the financial cost of managing these patients but evidence for this from randomised studies is lacking. The same optimism and caution can be extended to respiratory and cardiac complications of Duchenne muscular dystrophy.

Applicability of the results

Duchenne muscular dystrophy has a uniform course with regards to evolution of motor and function

disabilities. Most of the participants in the included studies were aged between 8 and 15 years. There were not enough data available to stratify the participants according to age and to observe the response to glucocorticoid corticosteroids in relationship to age. Data from the included studies and the non-randomised and cohort studies converge in suggesting a similar improvement and response to glucocorticoid corticosteroids in Duchenne muscular dystrophy. It is very likely that the results are applicable to all boys with Duchenne muscular dystrophy, especially in their ambulant phase. We would not anticipate that in the non-ambulant, wheel chair bound Duchenne patients who have been steroid-naive in the past, glucocorticoid corticosteroid treatment would produce a regained ability to walk. However, the benefit to upper limb, cardiac and respiratory function remains a possibility and this area needs further study.

The option of treatment with glucocorticoid corticosteroids should be discussed in detail with the parents of ambulant boys with Duchenne muscular dystrophy. It would be prudent to undertake this treatment only in centres with expertise and facilities for comprehensive multidisciplinary pre-treatment assessment and regular long-term monitoring of benefits and adverse effects. Protocols of management with close monitoring for adverse effects and adjustment of glucocorticoid dose would be an essential pre-requisite for patient safety.

Conclusion

The included randomised controlled trials show that glucocorticoid corticosteroids significantly improve muscle strength and function in the short-term (six months to two years) in Duchenne muscular dystrophy. Of the dose regimes tried, prednisolone 0.75 mg/kg/day is probably the most effective. Not enough data were available to compare efficacy of prednisone with deflazacort. What matters most is whether the beneficial effects seen over the short-term are maintained over the longer term and translate into prolongation of walking and preservation of pulmonary function. Data and evidence for this are only available from a few non-randomised cohort studies.

The excluded, non-randomised cohort studies suggested long-term (5 to 10 years) functional benefit, at least in some of the patients. A prolongation of walking ability was reported in many studies (Pandya 2001; Silversides 2003). Long-term pulmonary and cardiac benefits have been reported by one research group (Silversides 2003) and need to be confirmed. The increase in muscle strength upon initiation of treatment occurs over the first six months but this trend does not continue indefinitely. On continuation of glucocorticoids there may be stabilization for up to two years, followed by a decline, which may be slower as compared to natural history controls. The effective regime appears to be prednisone 0.75 mg/kg/day or the equivalent deflazacort dose of 0.9 mg/kg/day. These are the doses used for initiation of treatment. Expert opinion is that close monitoring of adverse effects and dose reduction is required over the long-term to ensure tolerability of the drug regime. Data from one small, randomised trial (Bonifati 2000) suggest an increased incidence and severity of weight gain with prednisone as compared to deflazacort. Data from non-randomised studies or randomised studies published only in abstract format suggest that weight gain as an adverse effect, is more frequent with prednisolone as compared to deflazacort. The effect of dietary advice and intervention as a co-intervention cannot be ruled out as confounding factors in this analysis. Data from non-randomised studies (Biggar 2001; Silversides 2003) and one randomised but unpublished trial (Reitter 1995) suggest a very high incidence of cataracts with deflazacort, a small number of which may require surgical intervention. The intermittent regimes (Connolly 2002; Dubowitz 2002) are postulated to have a better safety profile with regards to adverse effects but the efficacy has not been proven in randomised controlled trials. Open and cohort studies of the intermittent regimes have not documented prolongation of time to loss of walking. The age or functional stage of Duchenne muscular dystrophy at which glucocorticoid corticosteroids cease to be of benefit and the risks of adverse effects have not been determined.

Future studies

Criteria for acceptable clinical trials (Dubowitz 1980) and the methodology and importance of power calculations for therapeutic trials in Duchenne dystrophy (Brooke 1983) have been described. Reitter 2002

suggested 13 crucial points for the structure of clinical trials. The present review identifies the need for standardized and comparable protocols of assessment, timely publication of studies and the provision of sharing individual patient data on an anonymized basis, to facilitate future systematic reviews. In particular, there is a need for randomised controlled trials to discover the optimum dose, regimen and age to start treatment and the optimum dose regimen and type of glucocorticoid corticosteroid. National and international collaboration would help this effort. The incorporation of patients' and their parents' evaluation of the beneficial and adverse effects of treatment as additional outcome measures should be considered. The impact of glucocorticoid corticosteroid therapy on quality of life of the patient and the family, both in context of benefits and adverse effects, should be evaluated and formal assessment of quality of life is a desirable addition to future studies.

Conclusions

Implications for practice

Randomised controlled trials show that treatment with glucocorticoid corticosteroids in Duchenne muscular dystrophy improves muscle strength and function for six months to two years, and respiratory muscle strength and function for six months. The most effective prednisolone regime is probably 0.75 mg/kg/day. Not enough data were available to compare the efficacy of prednisone and deflazacort. The long-term benefits and harms are not clear but non-randomised studies suggest that potential harms are significant, including weight gain, behavioural changes, vertebral fractures and cataracts.

Implications for research

Many issues including the ideal age/functional stage for initiation of treatment, the optimal glucocorticoid regime, strategies for prevention of osteoporosis and the age for discontinuation of glucocorticoid treatment still need to be clarified with randomised controlled trials. This will need national and international collaboration, standardized and comparable protocols of assessment, timely publication of studies and the facility of sharing individual patient data. The feasibility of long-term placebo controlled glucocorticoid corticosteroid trials needs to be addressed from ethical and parental perspectives. While previous studies have focused mainly on the muscle strength, walking and motor aspects, respiratory, cardiac and quality of life issues need further investigation. There is a need to identify and research strategies to prevent predictable adverse effects of long-term glucocorticoid corticosteroid treatment, particularly osteoporosis and growth retardation.

Internal sources of support to the review

* Hammersmith Hospital UK

External sources of support to the review

*

Potential conflict of interest

Dr Adnan Y Manzur, at the time of preparation and submission of the protocol for this review was the principal investigator of a proposed UK multicentre trial of prednisolone in Duchenne muscular dystrophy. However, this trial was not funded. Currently, Dr Manzur is the lead clinician of the UK North Star Clinical Network for Neuromuscular Disorders. The clinicians on this clinical network have a consensus on approach to use of glucocorticoid corticosteroids (prednisolone) and plans for future collaboration to audit and modify clinical practice in line with available evidence.

Dr Mike Pike, at the time of preparation and submission of the protocol for this review, was a co-investigator for the proposed UK multicentre trial of prednisolone in Duchenne muscular dystrophy.

Dr Thierry Kuntzer has no conflicts of interest.

Dr Tony Swan has no conflicts of interest.

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Group co-ordinating editor, was instrumental in completion of this review.

Contribution of Reviewer(s)

AM wrote the first draft, selected the studies, assessed their methodological quality and extracted the data which was checked by the review group co-ordinator. TK selected the studies and assessed their quality. AS gave statistical advice and help with inference of data. All four authors (AM, TK, MP, AS) approved the final text.

Most recent changes

An update of this review to incorporate data from the newly published trial referenced in studies awaiting assessment is underway.

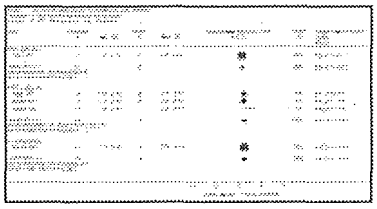
Synopsis

Glucocorticoid corticosteroid therapy in Duchenne dystrophy improves muscle strength and function for six months to two years

Duchenne muscular dystrophy is an incurable disease of childhood. Muscle wasting and loss of ability to walk lead to wheelchair dependence and eventually death. The precise way that glucocorticoids increase strength is unknown. Randomised controlled trials showed that glucocorticoid corticosteroids improved muscle strength and function for six months to two years. Short-term side effects were significant but not severe and could be managed. The long-term benefit remains unclear and has to be weighed against the long-term side effects of these drugs. Whether long-term trials to address this uncertainty are desirable should be addressed from ethical and parental perspectives.

Table of comparisons

Fig 01 Glucocorticoid corticosteroids versus placebo



01 MRC - Average muscle score - Prednisone

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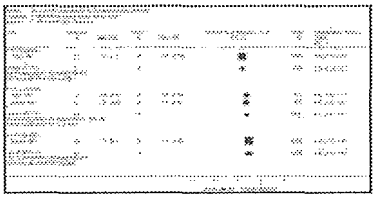

02 Lifting weight (kg) - Prednisone

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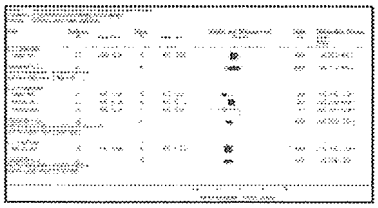

03 Time to rise to stand - Prednisone

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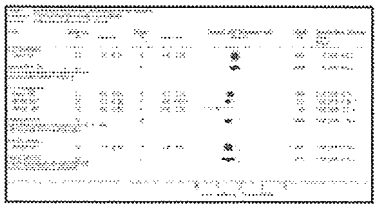

04 Nine metres walking time - Prednisone

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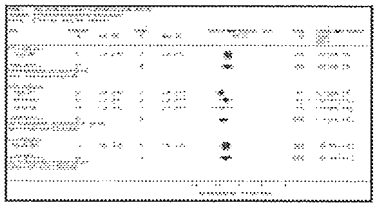

05 Four stairs climbing time - Prednisone

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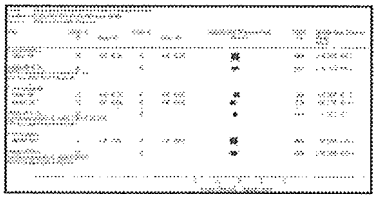

06 Leg function grade - Prednisone

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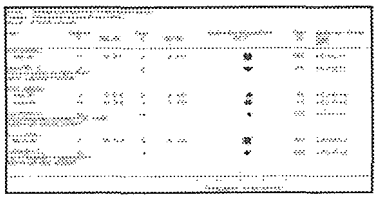

07 Forced vital capacity

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08 Mean % weight gain - Prednisone

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09 Mean % weight gain - Deflazacort 2 mg/kg alternate days

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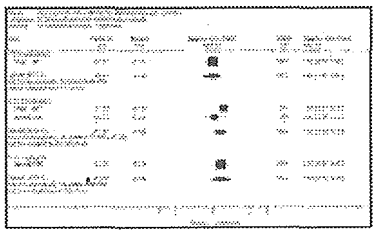

10 Behavioural changes - Prednisone

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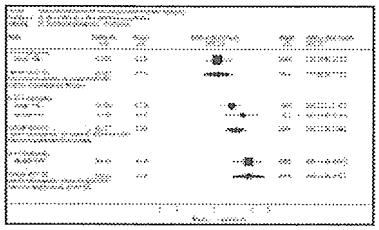

11 Cushingoid appearance - Prednisone

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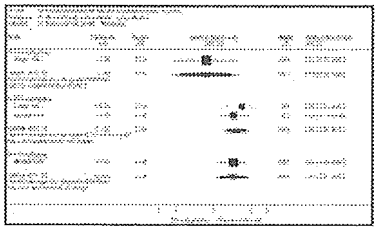

12 Excessive hair growth - Prednisone

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13 Acne - Prednisone

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Characteristics of included studies

Study: Angelini 1994

Methods: Randomised double blind trial. Randomisation followed 2:1 scheme.

Participants: 28 boys with DMD, all ambulant at entry in to the trial.

Interventions: Deflazacort 2 mg/kg on alternate days for 2 years or placebo.

Outcomes: Age at loss of ambulation, age at loss of ability to rise from floor, MRC index from 4 muscles.

Notes:

Allocation concealment: B

Study: Backman 1995

Methods: Randomised double blind crossover trial.

Participants: 37 boys with Duchenne MD (22 ambulant and 15 wheel chair dependent at entry to the trial), 4 boys with Becker MD.

Interventions: Prednisolone 0.35 mg/kg/day given for 6 months, then crossed over to placebo, or vice versa.

Outcomes: MRC score on 26 muscle groups, myometry on 24 muscle groups, modified Brooke and Scott scores, hand grip.

Notes:

Allocation concealment: B

Study: Griggs 1991

Methods: Randomised double blind, 2 treatment groups and 1 placebo group.

Participants: 99 boys with DMD, age range 5 to 15 years.

(70 of the 99 subjects were ambulant, either independently or in calipers, at entry to the study; 48 of the 67 in the prednisone groups and 22 of the 32 in the placebo group were ambulant).

Interventions: Prednisone 0.75 mg/kg/day for 6 months or prednisone 0.3 mg/kg/day for 6 months or placebo for 6 months.

Outcomes: Muscle strength reported as muscle strength score, based on grading of 34 muscle groups on 10-point modified Medical Research Council (MRC) score, lifting weights, timed 9- metre walk, climbing 4 stairs and rising from lying to standing, leg functional grades, and forced vital capacity (Brooke 1981, Mendell 1998)

Notes: Multicentre national trial

Allocation concealment: B

Study: Mendell 1989

Methods: *Randomised double blind with 3 groups.*

Participants: 103 boys with DMD aged 5 to 15 years.

(85 of the 102 subjects were ambulant, either independently or in calipers, at entry to the study; 55 of the 69 in the prednisone groups and 30 of the 33 in the placebo group were ambulant).

Interventions: Prednisone 0.75 mg/kg/day or prednisone 1.5 mg/kg/day or placebo for 6 months.

Outcomes: Muscle strength reported as muscle strength score, based on grading of 34 muscle groups on 10-point modified Medical Research Council (MRC) score, lifting weights, timed 9-metre walk, climbing 4 stairs and rising from lying to standing, leg functional grades, and forced vital capacity (Brooke 1981, Mendell 1998).

Notes: Multicentre national trial

Allocation concealment: B

Study: Rahman 2001

Methods: Randomised parallel groups.

Participants: 19 subjects with DMD.

(16 of the 19 subjects were ambulant at entry to the study; 8 of the 10 in the prednisolone group and 8 of the 9 in the control group were ambulant).

Interventions: Prednisolone 0.75 mg/kg/day for 6 months or placebo.

Outcomes: Muscle strength score, 30-ft walking, lying to standing time, 4- stair climbing times, and functional scores (Brooke 1981).

Notes:

Allocation concealment: A

* The authors of one study (Rahman 2001) provided information indicating adequate allocation concealment.

Characteristics of excluded studies

Study: Ahlander 2003

Reason for exclusion: Retrospective study.

Published as abstract only.

Study: Angelini 1995

Reason for exclusion: Non-randomised study.

Published as abstract only.

Study: Aviles 1982

Reason for exclusion: Non-randomised study.

Published as abstract only.

Study: Biggar 2001

Reason for exclusion: Non-randomised study.

Study: Bonifati 2000

Reason for exclusion: Randomised study of prednisolone vs deflazacort.

No placebo group to allow evaluation of glucocorticoid corticosteroid against placebo.

Study: Bothwell 2003

Reason for exclusion: Retrospective case note review and telephone interview study.

Study: Brooke 1987

Reason for exclusion: Non-randomised open study.

Study: Brooke 1996

Reason for exclusion: Randomised, double blind study

Published as an abstract only.

Full study not published and data not availalbe from the investigator.

Study: Campbell 2003

Reason for exclusion: Systematic online review of deflazacort in Duchenne muscular dystrophy.

Study: Connolly 2002

Reason for exclusion: Non-randomised study, historical controls.

Study: DeSilva 1987

Reason for exclusion: Non-randomised study.

Study: Drachman 1974

Reason for exclusion: Non-randomised open study.

Study: Dubowitz 2002

Reason for exclusion: Non-randomised open study.

Study: Dubrovsky 1999

Reason for exclusion: Non-randomised study.

Published as abstract only.

Study: Fenichel 1991a

Reason for exclusion: Three randomised groups (prednisone 0.75 mg/kg/day vs prednisone 1.5 mg/kg/day vs placebo) from previous Mendell 1989 study were all put on alternate-day prednisone, wihout breaking the randomisation code. There was no washout period between the two studies. All patients went on to alternate-day prednisone treatment and there was no contemporary placebo control group.

Study: Fenichel 1991b

Reason for exclusion: Open study on previous cohort of patients from Mendell 1989 and Fenichel 1991a Archives of Neurology studies.

Study: Griggs 1993

Reason for exclusion: Randomised study with prednisone group compared with azathioprine.

No placebo group.

Study: Kinali 2002

Reason for exclusion: Non-randomised, case series of 4 patients.

Study: Merlini 2003

Reason for exclusion: Non-randomised, open, parallel group study.

Study: Mesa 1991

Reason for exclusion: Non-randomised, double blind controlled study

"Two groups of 14 patients each were formed after an initial evaluation designed to balance the scores and composition of the groups."

Study: Pandya 2001

Reason for exclusion: Non-randomised, long-term cohort follow up of patients from Clinical investigation of Duchenne muscular dystrophy therapeutic trials (Mendell 1989, Griggs 1991) at University of Rochester.

Published as abstract only.

Study: Reitter 1995

Reason for exclusion: Randomised study of prednisolone vs deflazacort

Study reported in abstract format and at ENMC workshops, but no data available from investigators.

Study: Resende 2001

Reason for exclusion: Non-randomised, cohort study.

Published as abstract only.

Study: Sansome 1993

Reason for exclusion: Non-randomised open study.

Study: Siegel 1974

Reason for exclusion: Non-randomised study.

Clinically matched double blind evaluation.

Study: Silversides 2003

Reason for exclusion: Non-randomised study.

Retrospective cohort study.

Study: Todorovic 1998

Reason for exclusion: Randomised study.

Published as abstract only and data not available from the author.

Study: Tunca 2001

Reason for exclusion: Non-randomised cohort study.

Published as abstract only.

Study: Vasanth 1996

Reason for exclusion: Interim results of a randomised study of prednisone, ayurvedic medicine, and placebo, published as an abstract. Further unpublished data were provided by colleagues at Dr Vasanth's Instituition as she had demised. Study design was modified during the trial with amalgamation of the placebo control group with the ayurvedic treatment group. At completion of the study, prednisolone group was compared with ayurvedic drug treatment group. (See table of excluded randomised studies for more details).

Study: Wong 2002

Reason for exclusion: Evidence-based review of previous studies.

Study: de Groot 2002

Reason for exclusion: Non-randomised cohort study.

Table 01 Jadad scores - included studies

Study: Angelini 1994

Jadad Score: 3

Notes:

Study: Backman 1995

Jadad Score: 4

Notes:

Study: Griggs 1991

Jadad Score: 4

Notes: Drop-outs described in a subsequent study (Griggs 1993)

Study: Mendell 1989

Jadad Score: 4

Notes:

Study: Rahman 2001

Jadad Score: 3

Notes: On request, authors provided data on randomisation and description of drop-outs to the reviewers.

Table 02 Excluded non-randomised studies

Study ID: Drachman 1974

Design: Open

No of patients: 14

Age (years): 4 to 10.5

Regimen: Prednisone 2mg/kg/day for 3 months.

Then 2/3rds dose on alternate days.

Treatment period: 3 weeks to 28 months

Outcome: Improvement.

Adverse events: Side effects in 4 patients.

Study ID: Siegel 1974

Design: Double-blind

No of patients: 14

Age (years): 6 to 9

Regimen: Prednisone 5mg/kg on alternate days

Treatment period: 24 months

Outcome: No benefit.

Adverse events:

Study ID: Brooke 1987

Design: Open

No of patients: 33

Age (years): 5 to 15

Regimen: Prednisone 1.5mg/kg/day

Treatment period: 6 months

Outcome: Improvement.

Adverse events: 6 dropouts.

Study ID: DeSilva 1987

Design: Open

No of patients: 16

Age (years): 3 to 10

Regimen: Prednisone 2mg/kg/day for 3 months, then 2/3rds dose on alternate days

Treatment period: 1 to 11 months

Outcome: Walking prolonged by 2 years.

Adverse events: Excessive weight gain in 12 patients.

Cataracts in 2.

Study ID: Fenichel 1991b

Design: Open

No of patients: 92

Age (years): 5 to 15

Regimen: Prednisone 0.75mg/kg/day

Treatment period: 2 years.

Outcome: Stabilisation for 2 years. Prednisone 0.56mg/kg/day least effect dose.

Adverse events: Cataracts in 10 patients.

Glycosuria in 10 patients.

Significant weight gain.

Study ID: Mesa 1991

Design: Double-blind

No of patients: 28

Age (years): 5 to 11

Regimen: Deflazacort 1mg/kg/day

Treatment period: 9 months

Outcome: Improved till 6 months, then stable.

Adverse events: 35% cushingoid.

No significant weight gain.

Study ID: Sansome 1993

Design: Open

No of patients: 32

Age (years): 6 to 14

Regimen: Prednisolone 0.75mg/kg/day for 10 days/months.

10 days on 20 days off.

Treatment period: from 6 to 18 months

Outcome: Strength improved at 6 months.

Slow decline at 18 months.

Adverse events: Less side effects, but

26% of boys had more than 20% weight gain.

Study ID: Biggar 2001

Design: Open

No of patients: 30

Age (years): 7 to 15

Regimen: Deflazacort 0.9mg/kg/day

Treatment period: 3.8 years (+/-SD 1.5)

Outcome: Ambulation prolonged.

FVC preserved.

Adverse events: Cataracts in 30%.

Study ID: Dubowitz 2002

Design: Open

No of patients: 2

Age (years): 3 yrs 10 monhs

Regimen: Prednisolone 0.75mg/kg/day, given 10 days on and 10 days off

Treatment period: 5 years

Outcome: Stabilization of motor function for up to 5 years.

Adverse events: Irritability in 1 patient.

Study ID: Connolly 2002

Design: Open, historical controls

No of patients: 20 treated

Age (years): 5 to 10

Regimen: Prednisolone 5mg/kg twice weekly

(every Friday and Saturday)

Treatment period: 22 (+/- 1.5 months)

Outcome: Improved strength over 6 to 12 months in majority.

Adverse events: Irritability in 6. 2 stopped, 4 reduced prednisone dose.

Study ID: Merlini 2002

Design: Open, parallel group, double consent

No of patients: 5 treated, 3 control

Age (years): 2 to 4

Regimen: Prednisone

0.75/mg/kg for 2 weeks, then, 1.25mg/kg on alternate days

Treatment period: 47 to 63 months

Outcome: Ability to rise floor prolonged.

Stairs and 10m walking time similar.

Adverse events: Growth rate decline.

Irritability, requiring niaprazine in 1 patient.

Study ID: Kinali 2002

Design: Open

No of patients: 4 (including 2 patients from Dubowitz 2002)

Age (years): 3 yrs 10 months to 4.5 years

Regimen: Prednisolone 0.75mg/kg/day, given 10 days on and 10 days

Treatment period: 2.5 - over 5 years

Outcome: Stabilization of motor function for up to 5 years.

Loss of ambulation in 1 boy at age 9 years, after 5 years of treatment.

Adverse events: Bone mineral density on DEXA scans at 1-6 years of treatment was normal.

Study ID: Silversides 2003

Design: Retrospective cohort study.

Patients refusing treatment form control group.

No of patients: 33 (21 treated)

Age (years): 8.4 (+/-2)

Regimen: Deflazacort

Start: 0.9 mg/kg/day.

Gradual decrease in dose with age.

At 18 years: 0.59 +/-0.15mg/kg/day

Treatment period: 5.1 +/- 2.4 years

Outcome: Walking prolonged, 48% ambulant at 14 +/- 2 years of age.

Mean % predicted FVC

83% in treated, 41% control group.

Cardiomyopathy

5% of deflazacort versus 58% of controls.

Adverse events: Marked retardation of height gain.

Weighted gain similar to controls.

Cataracts in 50% (asymptomatic).

Study ID: Aviles 1982

(Published as abstract only)

Design: Open

No of patients:

Age (years):

Regimen: Prednisone

3 mg/kg on alternate days

Treatment period:

Outcome:

Adverse events:

Study ID: Dubrovsky 1999

(Published as abstract only)

Design: Open

No of patients: 30

(compared to 59 age matched controls)

Age (years): 7 - 21 yrs

Regimen: Deflazacort

0.5 - 1 mg/kg/day

Treatment period: 2 - 9 years

Outcome: Forced vital capacity significantly preserved in deflazacort treated group.

Adverse events: Not described.

Study ID: O'Tunca 2001

(Published as abstract only)

Design: Open

No of patients: 66

(compared with 22 historical controls)

Age (years): 2.5 - 11 years

Regimen: Prednisolone 0.75mg/kg on alternate days.

Vit D

Treatment period: 0.5 - 5 years

(mean 2.75)

Outcome: Mean age at loss of ambulation - prednisolone 10 years, controls 7.69 years)

No scoliosis at a mean age of 11 .7 years.

Adverse events: Not described

Study ID: Pandya 2001

(Published as abstract only)

Design: Open

No of patients: 13 independently ambulant patients from CIDD studies

Age (years):

Regimen: Prednisone

0.75 mg/kg/day,

gradually decreased over time

Treatment period: 10 years

Outcome: Mean age of loss of ambulation prolonged to 14.5 years.