学会名：　日本小児神経学会

医薬品名：　プレドニゾロン

6．参考情報	
	根拠となる論文・試験については、別表に記載願います。

学会名：　日本小児神経学会

医薬品名：　プレドニゾロン

７．連絡先	貴学会名、御担当者、御所属、御連絡先（住所、電話番号、FAX 番号、E-mail アドレス）等 担当者：大澤真木子、石垣景子 所属：東京女子医科大学小児科 連絡先： 住所　東京都新宿区河田町 8-1 電話番号　03-3353-8112 内 37308 FAX 番号　03-5379-1440 E-mail　mosawa@ped.twmu.ac.jp　大澤真木子 ＿＿＿＿＿＿＿＿＿＿＿＿　石垣景子

番号	学会名	販売名	一般名	文献題名	著者名	文献発表先、発表年	参考	文献の概要	学会見解
1	日本小児神経学会	経口	グルココルチコイド	Glucocorticoid corticosteroids for Duchenne muscular dystrophy	Cochrane Neuromuscular Disease Group. Adnan Manzur, Dubowitz Neuromuscular Centre, Department of Paediatrics, Hammersmith Hospital, DuCane Road, London, W12 OHS,	The Cochrane Library, Copyright 2005, The Cochrane Collaboration, Date of Most Recent Update: 20-May-2005		1月 to 2003年10月), EMBASE (1980年1月から 2003年10月), CINAHL and LILACS (1982年1月 から 2003年10月)も検索した。論文の著者にも手紙を書いて参考になるものをおしえてくれるよう依頼した。また適切な雑誌の抄録をさがした。選択基準：無作為割付あるいは準無作為割付の治験。参加患者はDMD。使用薬剤は、糖質コルチコイド prednisone, prednisolone, deflazacort その他で、使用期間が、最低3か月以上のもの。効果判定には、第一に独立歩行期間の予後、第二にMedical Research Council strength scoresを用いた徒手力テスト、機能予後と有害事象である。主な結果歩行期間の延長を判定に用いた小規模研究では有意な効果はみとめなかった。Secondary outcome measures: 3つの無作為割付試験 のmeta-analysisで、glucocorticoid corticosteroidsは筋力と機能を6か月以上 改善した。 立ち上がり時間、９ｍ歩行所要時間, 4段の階段のぼり所要時間を改善し、物を持ち上げる力、 下肢機能レベル、肺活量 を改善した。１無作為割付試験でglucocorticoid、corticosteroids は筋力を2年間安定させた. 最も有効な投与量は 0.75 mg/kg/日である。 deflazacortとprednisone を比較する十分な効果はない。有害事象：体重増加、行動異常、Cushing様外観は glucocorticoid、corticosteroidでplaceboに比べて高頻度に認められた。. 長期投与に伴う有害事象は短期試験なので評価不可能であった。非無作為試験についても効果と有害事象を検討した。二重盲検無作為割付試験でglucocorticoidcorticosteroid 治療は Duchenne 型筋ジストロフィーの筋力と機能を短期間 (6-2年)は改善し、最も効果的な投与量は、0.75 mg/kg/日である。有害事象は出現するが、短期間では重篤ではない。長期投与の効果と副作用の状況については現在の無作為試験からは評価できない。非無作為試験も機能改善が示されているが同時に長期投与では有害事象もある。長期投与の臨床的有用性については検討が必要である。	Evidenceとして認められるcochran libraryに採用された事は世界的にも有用と認められたこととなる

参考文献一覧

別表

番号	学会名	販売名	一般名	文献題名	著者名	文献発表先、発表年	参考	文献の概要	学会見解
2	日本小児神経学会	経口	グルココルチコイド	(Practice parameter: corticosteroid treatment of Duchenne dystrophy: report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Societ	UK. Phone: 0208 383 3295, Fax: 0208 383 2473, E-mail: a.manzur@ic.ac.uk, GB.	Neurology. 2005 Jan 11;64(1):13-20.		米国神経学アカデミー(AAN)、小児神経学会(CNS)のガイドラインの根拠となっている。この報告は1966年から2004年までのDMDと糖質コルチコイド治療に関する25の報告を、治療、経過観察期間とプレドニゾン(predonison)の投与量によりいくつかのグループに分け評価を行った。評価は筋力、尿中クレアチン量（筋量）、階段昇降、走行、起立にかかる時間による運動機能評価、肺機能検査により行われた。いずれのグループも糖質コルチコイド（プレドニゾン、プレドニゾロン）投与群の方がプラセボ群に比較して、明らかな有意差をもって改善が認められた。高用量群の方が低用量軍より、有為差のある効果を認めたが、一方で副作用の出現率（体重増加、尿糖、白内障など）が有意に認められた。結論として0.75mg/kg/日投与が最も副作用が少なく効果的な結果が得られる投与量として推奨された。	米国神経学アカデミー(AAN)、小児神経学会(CNS)のガイドラインにてプレドニゾン（predonisone）0.75mg/kg/日内服、体重増加、尿糖などの副作用出現時には0.30mg/kg/日へ減量する方針が推奨されている。
3	日本小児神経学会	経口	グルココルチコイド	デュシェンヌ型筋ジストロフィーの薬物療法一特に副腎皮質ホルモンについて	姜ら	臨床神経 36：1338-1340、1996		7歳代のデュシェンヌ型筋ジストロフィー児1mg／kg／隔日投与した。投与期間は120-240週。EST治験で偽薬を投与されたカンジの経過と比較して経過は有意に良好であった。	専門家の間では、少なくとも2　年間は有効と言う評価であり、欧米よりも少量で効果があるという期待が持たれた。

参考文献一覧

番号	学会名	販売名	一般名	文献題名	著者名	文献発表先、発表年	参考	文献の概要	学会見解
4	日本小児神経学会	経口	グルココルチコイド	筋ジストロフィーのプレドニン療法	炭田ら	平成8-10年度　厚生省精神／神経研究委託費筋ジストロフィーの遺伝相談及び全身的病態の把握と対策に関する研究班。研究報告書（班長石原伝幸）		DMD 10例、Becker 型2例、顔面肩甲上腕型1名にプレドニンを投与した。量は0.24-1.01mg/kg/隔日で、期間は4-36カ月。プレドニン開始10-から2週間で客観的、主観的改善が出現した。投与量による改善度の顕著な差はなかった。起坐時間に関しては効果の最長持続は33ヶ月、起立時間では約12-18ヶ月であった。一時中止による所用時間の延長および再開による同短縮を認めた。DMDではステージII階段昇降可能に開始した症例中4例が、平均歩行喪失年齢を超えて歩行可能で、内1例は11歳6ヶ月で歩行不能となった。ステージIV以降開始例では、運動機能所要時間の短縮が認められも歩行可能期間の延長は得られなかった。重篤な副作用はなかった。CRは開始後1-5ヶ月は減少し、以降前値に、戻る例、減少した値が時続する例など様々であった。投与量によるCR減少の程度は一定しなかった。CR変動と改善度の関連は明らかでなかった。プレドニン投与による短期効果は明らかであるが、長期予後への影響はなお不明である。今後至適投与量、方法、投与期間、開始年齢につき更に検討を要すると思われた。	

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Glucocorticoid corticosteroids for Duchenne muscular dystrophy

[Review]

Manzur, AY; Kuntzer, T; Pike, M; Swan, A

Date of Most Recent Update: 20-May-2005

Date of Most Recent Substantive Update: 24-December-2003

Cochrane Neuromuscular Disease Group.
Adnan Manzur, Consultant Paediatrician with Special Interest in Paediatic Neurology and Honorary Senior Lecturer, Dubowitz Neuromuscular Centre, Department of Paediatrics, Hammersmith Hospital, DuCane Road, London, W12 OHS, UK. Phone: 0208 383 3295, Fax: 0208 383 2473, E-mail: a.manzur@ic.ac.uk, GB.

Abstract

Background: Duchenne muscular dystrophy is the most common muscular dystrophy of childhood. This incurable disease is characterised by muscle wasting and loss of walking ability leading to complete wheelchair dependence by 13 years of age. Prolongation of walking is one of the major aims of treatment.

Objectives: The aim of this review was to assess whether glucocorticoid corticosteroids stabilize or improve muscle strength and walking in boys with DMD.

Search strategy: We searched the Cochrane Neuromuscular Disease Group specialised register (October 2003) using the term 'Duchenne muscular dystrophy'. We also searched MEDLINE (January 1966 to October 2003), EMBASE (January 1980 to October 2003), CINAHL and LILACS (January 1982 to October 2003). We wrote to authors of published studies and other experts in this disease to help identify other trials, checked the references in the identified trials and handsearched the abstracts of relevant journals.

Selection criteria:

Types of studies: randomised or quasi-randomised trials.
Types of participants: all patients with a definite diagnosis of Duchenne muscular dystrophy.
Types of interventions: glucocorticoids such as prednisone, prednisolone, deflazacort or others, with a minimum treatment period of three months.
Primary outcome measure: prolongation of walking (independent walking without long leg calipers).
Secondary outcome measures: strength outcome measures, manual muscle strength testing using Medical Research Council strength scores, functional outcome measures and adverse events.

Links

Abstract
Complete Reference

Outline

Data collection and analysis: We identified five randomised controlled trials that met the inclusion criteria for our review. Two reviewers independently selected the trials for the review and assessed methodological quality. Data extraction and inputting were double-checked.

Main results: Primary outcome measure: data from one small study used prolongation of walking as an outcome measure and did not show significant benefit.

Secondary outcome measures: The meta-analysis of the results from three randomised controlled trials showed that glucocorticoid corticosteroids improved muscle strength and function over six months. Improvements were seen in time taken to rise from the floor (Gowers' time), nine metres walking time, four-stair climbing time, ability to lift weights, leg function grade and forced vital capacity. One randomised controlled trial showed that glucocorticoid corticosteroids stabilize muscle strength and function for up to two years. The most effective prednisolone regime appears to be 0.75 mg/kg/day. Not enough data were available to compare efficacy of prednisone with deflazacort.

Adverse effects: Excessive weight gain, behavioural abnormalities, cushingoid appearance and excessive hair growth were all more common with glucocorticoid corticosteroids than placebo. Long-term adverse effects of glucocorticoid therapy could not be evaluated because of the short-term duration of the randomised studies.

Non-randomised studies: a number of non-randomised studies with important efficacy and adverse effects data are tabulated and discussed.

Conclusions: There is evidence from randomised controlled studies that glucocorticoid corticosteroid therapy in Duchenne muscular dystrophy improves muscle strength and function in the short-term (six months to two years). The most effective prednisolone regime appears to be 0.75 mg/kg/day. In the short term, adverse effects were significantly more common but not clinically severe. Long-term benefits and hazards of glucocorticoid treatment cannot be evaluated from the currently published randomised studies. Non-randomised studies support the conclusions of functional benefits but also indicate clinically significant adverse effects of long-term treatment. These benefits and adverse effects have implications for future research studies and clinical practice.

Graphics

Recent History

Glucocorticoid corticoste...

Issue protocol first published

2002 Issue 3

Date of last minor update

21 January, 2004

Date new studies found but not yet included or excluded

01 January, 2005

Issue next stage

Issue 2, 2006

Issue review first published

2004 Issue 2

Background

Duchenne muscular dystrophy (DMD) has an incidence of 1 in 3500 male live births (Emery 1991) and is the most common muscular dystrophy of childhood. The disease is remarkable for its severity with loss of walking by 13 years and death in the late teens or twenties (Dubowitz 1995; Emery 2003).

Boys with DMD present with abnormal gait, inability to run and difficulty in rising from the floor, in the first five years of life. The combination of muscle weakness and contractures of the tendo Achilles and iliotibial bands leads to loss of walking at a mean age of 9.5 years (range 7 to 13 years). Once these boys become wheelchair bound, scoliosis develops in over 90 per cent. Subclinical cardiomyopathy is very common, but this becomes symptomatic only in about 20% of the patients, often in the second decade of life (Frankel 1976; Muntoni 2003). The late teen years are marked by progression of respiratory muscle weakness, nocturnal hypoventilation, respiratory failure and death in late teens or twenties in untreated patients. No curative treatment for DMD is known, but the quality of life and comfort of the patient can be improved by symptomatic physiotherapeutic and medical treatments (Bushby 2003; Dubowitz 1995; Emery 2003; Heckmatt 1989; Ishikawa 1995; Ishikawa 1999). Provision of respiratory support, with ventilator use at the appropriate stage, can prolong survival into the fourth decade (Eagle 2002; Gomez-Merino 2002; Jeppesen 2003).

The Duchenne muscular dystrophy gene locus is at Xp21 and codes for a protein named dystrophin (Hoffman 1987). Depending on the type of mutation in the dystrophin gene, there may be a severe reduction or absence of dystrophin in muscle, resulting in DMD (Koenig 1989). Dystrophin localises at the cytoplasmic side of the sarcolemma and binds to a glycoprotein complex (Matsumura 1993; Matsumura 1994; Mendell 1995). This dystrophin-glycoprotein complex provides a link between the cytoskeleton in the muscle fibre and the extracellular matrix. Lack of dystrophin compromises this link and is postulated to lead to muscle fibre degeneration (Petrof 1993; Petrof 1998). Though Duchenne dystrophy is not primarily an immune-mediated disease, there is evidence that raises the possibility of humoral and cellular immune responses contributing to the pathological processes. This includes invasion of necrotic muscle fibres by macrophages and cytotoxic T-cells (Arahata 1984), complement activation with deposition of membrane attack complexes on necrotic fibres, and expression of HLA class I antigens on the dystrophic muscle fibres (Engel 1982), making them susceptible to T-cell mediated damage. Initial empirical studies of prednisone in Duchenne dystrophy (Drachman 1974) and the above histopathological observations led to trials of immunomodulation therapy with corticosteroids (Angelini 1994; Backman 1995; Biggar 2001; Bonifati 2000; Dubowitz 2002; Fenichel 1991a; Fenichel 1991b; Griggs 1991; Griggs 1993; Mendell 1989; Mesa 1991; Sansome 1993), azathioprine (Griggs 1993) and cyclosporin (Sharma 1993) in Duchenne muscular dystrophy. cDNA microarray studies on the *mdx* mouse have demonstrated a differential gene expression in the affected and non-affected muscles (Porter 2003), and a "skeletal muscle molecular signature" dominated by chronic inflammatory response (Porter 2002). A recent study of cDNA microarray analysis of skeletal muscle from Duchenne muscular dystrophy patients (Noguchi 2003) reported a variable gene expression pattern which correlated with the severity of dystrophic changes on histological examination. These studies provide further evidence that the absence of dystrophin, though necessary, is not sufficient to cause the pattern of fibrosis, inflammation and muscle degeneration/regeneration characteristic of Duchenne muscular dystrophy.

Treatment with glucocorticoid corticosteroids has been claimed to result in stabilisation of strength for periods of up to three years (Fenichel 1991b). There are no long-term randomised studies demonstrating prolongation of ambulation. The commonly used corticosteroids in published trials are prednisone, prednisolone and deflazacort. The corticosteroid dose used in various trials for prednisolone, or its equivalent glucocorticoid dose, ranges from 0.3 mg to 1.5 mg/kg/day, given daily or on alternate days, or in an intermittent (ten days on, ten days off) regime. The precise mechanism by which glucocorticoids may increase strength in Duchenne dystrophy is not known but their potential beneficial effects include inhibition of muscle proteolysis (Ellis 1981; Rifai 1995), stimulation of myoblast proliferation (Bai 1980), increase in myogenic repair (Anderson 2000), anti-inflammatory/immunosuppressive effect (Kissel 1991), reduction of cytosolic calcium concentrations (Metzinger 1995; Passaquin 1998; Vandebrouck 1999) and up regulation of utrophin (Pasquini 1995).

Whilst the potential value of steroids in the treatment of DMD has been acknowledged by international collaborative workshops (Dubowitz 1997; Dubowitz 2000), there are uncertainties about the use of glucocorticoid treatment in Duchenne muscular dystrophy and no clear guidelines are available to the clinician (Dubrovsky 1998; Manzur 2001). Although a beneficial effect on muscle strength is claimed by many researchers, the long-term functional benefit remains unclear and has to be weighed against the short- and long-term side effects and tolerability of these drugs.

Objectives

The aim of this review was to assess whether glucocorticoid corticosteroids stabilize or improve muscle strength and walking in boys with DMD, and whether the steroid regimes can be tolerated for long enough to make a biologically significant difference in the natural history of the condition. Available evidence on the optimally effective dose with minimal side effects, and on how long the therapeutic effects last, were to be summarized.

Criteria for considering studies for this review

Types of participants

We considered all patients with a definite diagnosis of Duchenne muscular dystrophy, based on:

(1) the definition of Brooke et al. (Brooke 1981).
Male patient with onset of proximal weakness by five years, elevated serum creatine kinase (CK), together with two of the following minor criteria: muscle hypertrophy/lower limb contractures, electrocardiogram (ECG) changes, myopathic electromyogram (EMG) changes, dystrophic change on muscle biopsy.
or
(2) the European Neuromuscular Centre (ENMC) DMD diagnostic criteria (Emery 1997).
Onset of proximal weakness by five years of age, loss of unassisted walking by 13 years, 10-fold or greater elevation of serum CK, dystrophic muscle biopsy, absent or almost no dystrophin on muscle biopsy, and / or Duchenne-type mutation in the dystrophin gene.

Types of intervention

Drug therapies reviewed were glucocorticoid corticosteroids including:

* prednisone;
* prednisolone;
* deflazacort;
* any other glucocorticoid if identified.

The minimum treatment period was three months. The three drugs were reviewed as a group to analyse the effect of corticosteroids on patients with DMD. The glucocorticoids were reviewed on the basis of their dose equivalence, which is well known (BNF 2001; Frey 1990).

Types of outcome measures

Primary outcome measure

Prolongation of time to loss of walking [independent walking without long leg calipers (Heckmatt 1985; Spencer 1962)].

Secondary outcome measures

(1) Strength outcome measures (performed after an intervention period of at least three months).
Manual muscle strength testing using Medical Research Council (MRC) strength scores (MRC 1976).
(2) Functional outcome measures.
Functional rating scores such as Motor Ability Score (Scott 1982) and Functional score (Brooke 1981; Brooke 1983).
Walking times such as time taken to walk 30 feet (Brooke 1981; Brooke 1983; Scott 1982).

(3) Adverse events (noted during treatment or up to one year after cessation of treatment):

* deaths;

* life threatening infections;
* fractures (if data were available beyond one year after cessation of treatment they were collected);
* abnormal behaviour such as irritability, hyperactivity, euphoria, mood lability, depression;
* hypertension;
* weight gain;
* cataracts;
* other disabling adverse effects.

Types of studies

We considered all randomised or quasi-randomised trials of glucocorticoids such as prednisone, prednisolone, deflazacort or others, with a minimum treatment period of three months. Quasi-randomised trials are those using a method of allocating participants to different forms of care that is not truly random such as allocation by date of birth, day of the week or medical record number.

Search strategy for identification of studies

A search for trials in DMD on the Cochrane Neuromuscular Disease Group specialised register was carried out (searched July 2002 and repeated October 2003) using the term 'Duchenne muscular dystrophy'. A similar search strategy was applied to MEDLINE (from January 1966 to October 2003), EMBASE (from January 1980 to October 2003), and CINAHL and LILACS (from January 1982 to October 2003). We wrote to authors of published studies and other experts in this disease to help identify other trials. All references in the identified trials were checked and authors contacted to identify any additional published or unpublished data or other trials.

Methods of the review

Study selection

One reviewer (AM) independently screened the initial search of all the databases and reference lists to identify citations with potential relevance to the review. The full text of selected articles (translated into English where required) was obtained and, using defined eligibility criteria, trials were selected for inclusion in the review. Reviewers were not blinded to authors, journal or results. Discussion between the authors and if necessary the involvement of a third party (editor in charge of the review), resolved disagreements when they occurred.

Two reviewers (AM, TK) independently assessed the quality of the trials to be included in the review.

Allocation concealment

Using the Cochrane approach to assessment of allocation concealment (Clarke 2003) all trials were scored using the following principles: Grade A: Adequate concealment, Grade B: Uncertain, Grade C: Clearly inadequate concealment, Grade D: Not done. 'Allocation concealment' refers to the process of concealing assignment until treatment has been allocated, thereby minimizing bias in allocation of participants to treatment or placebo group (

Quality assessment

Quality was also assessed using a five-part score (Jadad 1996) summarised below.
Was the study described as randomised? (1 = yes; 0 = no)
Was the study described as double blind? (1 = yes; 0 = no)
Was there a description of withdrawals and dropouts? (1 = yes; 0 = no)
Was the method of randomisation well described and appropriate? (1 = yes; 0 = no)
Was the method of double blinding well described and appropriate? (1 = yes; 0 = no)

Points were deducted for inadequate randomisation or blinding.

Data extraction

One reviewer, using a standard form, extracted the data from the selected trials. Full reports were sought from authors where trials were published in abstract form, presented at meetings or presented as posters, and reviewers contacted authors to obtain missing or ambiguously reported data. Because a

number of the published papers gave only p values and means or differences, the SDs and other quantities required for the Review Manager meta-analysis had to be inferred by inverting the p value calculations. Care was required by a statistician to obtain reasonable values from what were sometimes very small and 'rounded' p values.

Data analysis

Data were entered into Review Manager 4.2 (RevMan) by one reviewer (AM) and checked by the review group co-ordinator of the Cochrane Neuromuscular Disease Group. Where appropriate, estimates from individual studies were pooled to obtain overall estimates and 95% confidence intervals (95% CIs). For continuous outcome measures this was done using weighted differences between means (WMDs). For dichotomous outcomes rate ratios or relative risks (RRs) were used.

Statistical considerations

The possibility of heterogeneity of treatment-effect differences among studies was investigated with appropriate tests.

It was not possible to carry out subgroup analyses (e.g. for age at initiation of glucocorticoid corticosteroid: less than 7 years old or 7 years or older) as these data were not available for individual studies.

Description of the studies

Literature searches were undertaken in July 2002 and updated in October 2003. The databases searched and the number of possibly relevant references identified on each databases were as follows: Cochrane Neuromuscular Disease Group specialised register - 29 references, CINAHL - 0 references, LILACS- 0 references, MEDLINE - 91 references, EMBASE - 61 references. Hand searches of meeting abstracts and bibliographic checks identified another eight abstracts and one published study.

The full text of 26 possibly relevant studies and the abstracts of 11 further studies for which the completed trials have not been published were obtained and evaluated. For one study presented in scientific workshops but not published (Reitter 1995), the lead investigator was contacted but no data are yet available.

Fourteen studies, published in detail in peer-reviewed journals, were excluded because they were non-randomised (Biggar 2001; Bothwell 2003; Connolly 2002; DeSilva 1987; Drachman 1974; Dubowitz 2002; Fenichel 1991a; Fenichel 1991b; Kinali 2002; Merlini 2003; Mesa 1991; Sansome 1993; Siegel 1974; Saversides 2003). Two review articles (Campbell 2003; Wong 2002) reporting the various studies were identified and excluded. Eight studies published in abstract format only were non-randomised and excluded from the review (Ahlander 2003; Angelini 1995; Aviles 1982; de Groot 2002; Dubrovsky 1999; Pandya 2001; Resende 2001; Tunca 2001).

Eleven studies of glucocorticoid corticosteroid with randomisation methodology were identified (Angelini 1994; Backman 1995; Bonifati 2000; Brooke 1996; Griggs 1991; Griggs 1993; Mendell 1989; Rahman 2001; Reitter 1995; Vasanth 1996; Todorovic 1998).

Eight studies (Angelini 1994; Backman 1995; Brooke 1996; Griggs 1991; Mendell 1989; Rahman 2001; Todorovic 1998; Vasanth 1996) randomised glucocorticoid corticosteroids against placebo, five of which (Angelini 1994; Backman 1995; Griggs 1991; Mendell 1989; Rahman 2001) have been published in full detail in peer-reviewed journals. Lead investigators of the other three studies, published in abstract (Brooke 1996; Todorovic 1998; Vasanth 1996), were contacted for provision of data, but these data had been received for only one study (Vasanth 1996) by the time of publication of this review. Dr Vasanth had sadly passed away and data for the completed Vasanth 1996 study was forwarded to the reviewers by Dr Arun B Taly from the National Institute of Mental Health and Neuro Sciences, Bangalore. Vasanth 1996 did not meet the inclusion criteria for our analysis as the study design was modified during the trial with amalgamation of the placebo control group with the ayurvedic treatment group (*see* Table of characteristics of excluded studies and Additional Table 02 - excluded randomised studies).

Three randomised studies randomised glucocorticoid corticosteroids against another drug rather than placebo (Bonifati 2000; Griggs 1993; Reitter 1995). Reitter et al. (Reitter 1995) and Bonifati et al. (Bonifati 2000) randomised deflazacort against prednisone. Griggs et al. (Griggs 1993) randomised prednisone against azathioprine. These three studies did not meet the inclusion criteria for our analysis (*see* Table of characteristics of excluded studies).

Brooke et al. (Brooke 1996) randomised prednisone and deflazacort against placebo for three months and then randomised the placebo group to one of the treatment groups. Only the abstract has been published and data were not obtainable from the author. The study thus was not included in our analysis.

Randomisation with crossover design was used for one study (Backman 1995) and it was eligible for inclusion. We contacted the surviving authors who were not able to provide the data required for analysis.

Data from four double-blind studies with randomised parallel group methodology were available and included in this review (Angelini 1994; Griggs 1991; Mendell 1989; Rahman 2001). Overall, these studies comprised 249 participants, divided into 88 in the placebo groups and 161 in the glucocorticoid corticosteroid treatment groups. Seventy-one of the 88 participants in the control group and 128 of the 161 in the glucocorticoid corticosteroid groups were walking, either independently or with the help of long leg braces. The glucocorticoid corticosteroid treatment groups included prednisone (n = 134), prednisolone (n = 10) and deflazacort (n = 17).

Three of the included studies (Griggs 1991; Mendell 1989; Rahman 2001) used prednisone or prednisolone, in a daily dose regime, in the treatment groups. The duration of these three studies was six months. Prednisone is broken down in the body to prednisolone and they are equipotent in glucocorticoid effect (Azarnoff 1975; Frey 1990). The total number of participants in these three studies was 144 in the treatment group and 77 in the placebo group.

One included study (Angelini 1994) used deflazacort in the treatment group. Deflazacort was used in a dose of 2 mg/kg body weight on alternate days, for two years.

Only one study (Angelini 1994), with 28 participants, addressed the primary outcome measure of prolongation of walking.

The secondary outcome measures were assessed by different parameters and assessment tools in the four studies. However, the two studies (Mendell 1989; Griggs 1991) comprising 80% of the participants for all the four included and analysed studies used the same outcome measures, as described in Brooke 1981(*see* Characteristics of included studies).

Methodological qualities of included studies

Details of Jadad scoring for the included studies are presented in the Additional Tables section, Table 01. All studies were described as randomised but none described the method of randomisation. Four of the five studies were described as double blind, but only three described the method of blinding. Three of the five studies (Angelini 1994; Backman 1995; Mendell 1989) reported and described withdrawals and dropouts. One other study (Griggs 1991) described dropouts from their study in a subsequent sequential study (Griggs 1993). The fifth study (Rahman 2001) reported one dropout and described it in response to the Cochrane reviewer's request. Three studies (Backman 1995; Griggs 1991; Mendell 1989) scored 4 out of a maximum of 5 on the Jadad score. Two studies (Angelini 1994; Rahman 2001) scored 3 out of 5. The studies scoring 3 on the Jadad scale (Angelini 1994; Rahman 2001) contributed 47 participants to the total of 249 included in the analysis.

Only one study (Rahman 2001) was graded 'A' for allocation concealment and this was on the basis of information provided by the authors to the Cochrane reviewers. The other four included studies were graded 'B' for allocation concealment as this was not described in any of the reports (*see* Table of included studies).

Results

Primary outcome measure: prolongation of time to loss of walking

Only one of the randomised studies (Angelini 1994) used prolongation of time to loss of walking as an outcome measure. They studied 28 patients over a minimum follow-up period of 24 months. The other studies were of short duration (six months) and not designed to demonstrate prolongation of walking.

Angelini et al. (Angelini 1994) reported that deflazacort prolonged ambulation by 13 months, but the statistical technique used to infer this result was not appropriate. Four of the 17 participants in the deflazacort group became wheelchair bound, at a mean interval of 33.2 months after randomisation. Six of the 11 participants in the placebo group became wheelchair bound, at a mean interval of 20.5 months after randomisation. The validity of this inference is considered in the Discussion.

Secondary outcome measures

(1) Muscle strength

(a) Average muscle score

Muscle strength was assessed and reported as an average muscle score (Brooke 1981; Brooke 1983) in three studies (Griggs 1991; Mendell 1989; Rahman 2001). The two large studies (Griggs 1991; Mendell 1989) had three arms, with one placebo and two treatment groups. Mendell 1989 studied two prednisone dose regimes (0.75 mg/kg/day and 1.5 mg/kg/day) and compared them with one placebo group. Griggs 1991 also studied two prednisone dose regimes (0.3 mg/kg/day and 0.75 mg/kg/day) and compared them with one placebo group. Our analysis for treatment effect utilized the placebo groups twice. Backman et al. (Backman 1995) evaluated muscle strength in three ways: (a) average muscle strength was obtained by examining 26 muscle groups on the MRC 0 to 5 grading system and the performance scores were added and divided by the number of muscle groups to get the average muscle strength; (b) isometric muscle strength was measured in 24 muscle groups with a Penny and Giles myometer; (c) hand-grip strength was measured bilaterally with a strain gauge. The data were not reported in the published study and were not obtainable from the surviving author. Angelini et al. (Angelini 1994) measured muscle strength in two ways: (a) MRC index calculated by assessing four limb muscle groups using the MRC scale; (b) myometry was performed but the number of muscle groups tested and the myometer used were not described.

Analysis of pooled data from three trials (Griggs 1991; Mendell 1989; Rahman 2001) demonstrated a statistically significant improvement in average muscle score in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo, with a weighted mean difference (WMD) of 0.50 (95% CI 0.35 to 0.66) (see Graph Outcome 01 MRC - Average muscle score). The WMD is a method of meta-analysis used to combine differences between treatment effects from different studies when the outcomes are measured in the same units in each trial. It averages the differences from the studies involved in the meta-analysis, weighting them according to the size of the treatment groups in the various studies.

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo and after six months of treatment there was statistically significant improvement in average muscle score in favour of the prednisone group, with a mean difference of 0.34 (95% CI 0.17 to 0.51) (*see* Graph - Outcome 01 MRC - Average muscle score).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo and after six months of treatment there was a statistically significant improvement in average muscle score in the prednisone group, with a mean difference of 0.45 (95% CI 0.23 to 0.67) (*see* Graph -Outcome 01 MRC - Average muscle score).

(b) Ability to lift weights

Ability to lift standardized weights (Brooke 1981) was assessed and reported in two studies (Griggs 1991; Mendell 1989). Analysis of pooled data from these studies demonstrated a statistically significant improvement in lifting weights in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo, with a WMD of 0.75 (95% CI 0.50 to 0.99) (*see* Graph - Outcome 02 Lifting weight).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo and after six months of treatment there was a statistically significant improvement in lifting weights in the prednisone group, with a mean difference of 0.38 (95% CI 0.13 to 0.63) (*see* Graph - Outcome 02 Lifting weight).

Mendell 1989 compared prednisone 1.5 mg/kg/day with placebo and after six months of treatment there was a statistically significant improvement in lifting weights in the prednisone group, with a mean difference of 0.96 (95% CI 0.52 to 1.40) (*see* Graph - Outcome 02 Lifting weight).

(2) Functional benefits

(a) Time taken to rise from the floor (Gowers' time)

Time taken to rise to the standing position (Brooke 1981) was reported in three studies (Griggs 1991; Mendell 1989; Rahman 2001). Analysis of pooled data from these studies demonstrated statistically significant improvement in the prednisone 0.75 mg/kg/day group after six months of treatment, with a WMD of 2.47 (95% CI 1.57 to 3.37) seconds less than in the placebo group (*see* Graph - Outcome 03 Time to rise to stand).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment the mean time to rise to stand was 1.59 (95% CI 0.57 to 3.75) seconds less (*see* Graph - Outcome 03 Time to rise to stand) in the prednisone group.

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo. After six months of treatment the mean improvement in time to rise to stand was 2.74 (95% CI 1.5 to 3.98) seconds less in the prednisone group (*see* Graph - Outcome 03 Time to rise to stand).

(b) Nine-metre walking time

The time taken to walk nine metres (Brooke 1981) was reported in three studies (Griggs 1991; Mendell 1989; Rahman 2001). Analysis of pooled data from these studies demonstrated a statistically significant improvement in nine-metre walking time in the prednisone 0.75 mg/kg/day group after six months of treatment, with a WMD of 2.66 (95% CI 1.59 to 3.73) seconds less than in the placebo group (*see* Graph - Outcome 04 Nine metres walking time).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo and after six months of treatment the mean time was 1.18 (95% CI 0.30 to 2.66) seconds less in the prednisone group (*see* Graph - Outcome 04 Nine metres walking time).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo. After six months of treatment the mean time was 2.64 (95% CI 0.80 to 4.48) seconds less in the prednisone group (*see* Graph - Outcome 04 Nine metres walking time).

(c) Four-stairs climbing time

The time taken to climb four standardized stairs (Brooke 1981) was reported in three studies (Griggs 1991; Mendell 1989; Rahman 2001). Analysis of pooled data from these studies demonstrated a statistically significant improvement with a WMD of 3.72 (95% CI 2.65 to 4.78) seconds less in the prednisone 0.75 mg/kg/day group after six months of treatment (*see* Graph - Outcome 05 Four stairs climbing time).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo, and after six months of treatment the mean improvement was 2.68 (95% CI 1.30 to 4.06) seconds less in the prednisone group (*see* Graph - Outcome 05 Four stairs climbing time).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo and after six months of treatment the mean improvement in the prednisone group was 3.05 (95% CI 1.52 to 4.58) seconds less than in the control group (*see* Graph - Outcome 05 Four stairs climbing time).

(d) Leg function grade

Leg function grade (Brooke 1981; Brooke 1983) was assessed in two studies (Griggs 1991; Mendell 1989). The leg

function grade is assessed on a 10-point scale, grade 1 representing ability to walk and climb stairs without assistance and grade 10 representing confinement to bed. Analysis of pooled data from these studies demonstrated a statistically significant improvement in the prednisone 0.75 mg/kg/day group after six months of treatment, with a WMD of 0.41 (95% CI 0.11 to 0.70) less than in the placebo group (*see* Graph - Outcome 06 Leg function grade).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment the mean improvement in leg function grade was 0.39 (95% CI 0.01 to 0.79) less than in the placebo group (*see* Graph - Outcome 06 Leg function grade).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo and after six months of treatment the mean improvement in the prednisone group was 0.49 (95% CI 0.05 to 0.93) less than in the placebo group (*see* Graph - Outcome 06 Leg function grade).

(e) Pulmonary function - forced vital capacity

Forced vital capacity (Brooke 1981) was measured in two studies (Griggs 1991; Mendell 1989). Analysis of pooled data from these studies demonstrated a mean improvement in forced vital capacity in the prednisone 0.75 mg/kg/day group, after six months of treatment of 0.17 litres more than in the placebo group (95% CI 0.10 to 0.24) (*see* Graph - Outcome 07 Forced vital capacity).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment the improvement in forced vital capacity in the prednisone group was 0.16 (95% CI 0.05 to 0.27) of a litre more than in the placebo group (*see* Graph - Outcome 07 Forced vital capacity).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo. After six months of treatment the mean improvement in forced vital capacity in the prednisone group was 0.14 (95% CI 0.05 to 0.23) of a litre more than in the placebo group (*see* Graph - Outcome 07 Forced vital capacity).

Observations on trends in benefit with glucocorticoid corticosteroid dose

A proper investigation of the prednisone dose response relationship to identify the optimum dose would need individual patient data within study analyses, and no such analyses were reported. This is considered further in the Discussion. From the forest plots showing studies grouped by dosage of prednisone on several outcome variables, the impression is that the benefit increases as dose increases from 0.3 mg/kg/day to 0.75 mg/kg/day, but there is little evidence of an increase in benefit when the dose is further increased from 0.75 to 1.5 mg/kg/day. This suggests that the middle dosage is adequate to achieve what benefit prednisone can provide. This conclusion is partly confounded by study differences and such a visual inference must be treated with considerable caution.

(3) Side effects

Side effects were evaluated by the different investigators as follows.

Mendell 1989 examined the participants for side effects in an area separate from that of clinical evaluation at baseline and at one, two, three and six months after prednisone treatment was begun. Data for both treatment and placebo groups were reported.

Griggs 1991 examined the participants and interviewed the parents for side effects at baseline and at one, two, three and six months of treatment. Data for both treatment and placebo groups were reported.

Rahman 2001 did not report side effect data.

Angelini 1994 monitored the participants every two months of the study for side effects. Weight gain data were reported for treatment (deflazacort) and placebo groups but incidence of the other side effects was reported only for the deflazacort group.

Backman 1995 asked the parents of the participants at the end of the investigation (study) to report any signs or symptoms that could possibly be related to the treatment.

(a) Weight gain

Mendell 1989 and Griggs 1991 reported this adverse event as per cent of weight gained above baseline, comparing weight at first visit with weight at last visit (on the presumption of six months of treatment). As per cent of weight gain was only available as the number of participants in each of a set of intervals on the per cent weight gain scale, the mean and standard deviation for each group was derived assuming each individual had the mid-value of the interval in which they fell. Sheppard's correction for bias in variances obtained using grouped data was not used because the interval widths are variable and the magnitude of the correction for bias in the standard deviations was found to be less than 2%. Analysis of pooled data from Mendell 1989 and Griggs 1991 demonstrated a statistically significant weight gain in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo, with a WMD of 9.27% (95% CI 6.87% to 11.68%) (*see* Graph - Outcome 08 Mean % weight gain - prednisone).

Angelini 1994 compared deflazacort with placebo and presented weight gain data for 11 deflazacort and five placebo patients as per cent weight change. As per cent weight change was only reported as the number of participants in each of a set of intervals on the per cent weight gain scale, the mean and standard deviation for each group were derived as described above for Mendell 1989 and Griggs 1991. After two years of treatment, there was a trend to excessive weight gain in the deflazacort group but this was not statistically significant, with a mean difference of 1.09% (95% CI -13.92 to 16.10) (*see* Graph - Outcome 09 Mean % weight gain - deflazacort). Though this study is small in numbers, a statistically non-significant weight gain in the deflazacort group treated for two years is in marked contrast to the statistically significant weight gain in the prednisone groups treated only for six months in Mendell 1989 and Griggs 1991.

A comparison of prednisone with deflazacort with regards to weight gain could not be done because of different durations of treatment in prednisone studies (Mendell 1989; Griggs 1991; Rahman 2001 - six months) and deflazacort study (Angelini 1994 - two years).

(b) Behavioural changes

The number of patients with behavioural changes in treatment and placebo groups was reported in two studies (Griggs 1991; Mendell 1989). Analysis of pooled data from these studies demonstrated a significant risk of behavioural changes in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo, with a RR of 1.38 (95% CI 1.04 to 1.83) (*see* Graph - Outcome 10 Behavioural changes - prednisone).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment there was no statistically significant difference in behavioural changes in the prednisone and placebo groups, with a RR of 1.02 (95% CI 0.67 to 1.56) (*see* Graph - Outcome 10 Behavioural changes - prednisone).

Mendell 1989 compared prednisone 1.5 mg/kg/day with placebo. After six months of treatment there was a trend to increased risk of behavioural changes in the prednisone group but this was not statistically significant, with a RR of 1.43 (95% CI 0.92 to 2.24) (*see* Graph - Outcome 10 Behavioural changes - prednisone).

Angelini 1994 reported behavioural changes in 6 of 11 participants in the deflazacort group at six months but the data for the placebo group were not reported.

(c) Cushingoid appearance

The number of patients with cushingoid appearance in treatment and placebo groups was reported in two studies (Griggs 1991; Mendell 1989). Analysis of pooled data from these studies demonstrated a significant risk of cushingoid appearance in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo, with a RR of 2.46 (95% CI 1.58 to 3.84) (*see* Graph - Outcome 11 Cushingoid appearance - prednisone).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment there

was no significant difference in cushingoid appearance in the prednisone and placebo groups, with a RR of 1.15 (95% CI 0.60 to 2.17) (*see* Graph - Outcome 11 Cushingoid appearance - prednisone).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo, and after six months of treatment there was a significant risk of cushingoid appearance in the prednisone group, with a RR of 4.36 (95% CI 2.04 to 9.33) (*see* Graph - Outcome 11 Cushingoid appearance - prednisone).

Angelini 1994 reported a cushingoid appearance in 2 of 11 participants in the deflazacort group at six months but the data for placebo group were not reported.

(d) Excessive hair growth

The number of patients with excessive hair growth in treatment and placebo groups was reported in two studies (Griggs 1991; Mendell 1989). Analysis of pooled data from these studies demonstrated a statistically significant risk of excessive hair growth in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to the placebo group, with a RR of 2.66 (95% CI 1.50 to 4.72) (*see* Graph - Outcome 12 Excessive hair growth - prednisone).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo. After six months of treatment there was no significant difference in excessive hair growth in the prednisone and placebo groups, with a RR of 0.73 (95% CI 0.18 to 3.0) (*see* Graph - Outcome 12 Excessive hair growth - prednisone).

Mendell 1989 also compared prednisone 1.5 mg/kg/day with placebo, and after six months of treatment there was a significant increase in the number of boys with excessive hair growth in the prednisone group, with a RR of 2.32 (95% CI 1.16 to 4.65) (*see* Graph - Outcome 12 Excessive hair growth - prednisone).

Angelini 1994 reported excessive hair growth in none of the 11 participants at six months and in three out of eight patients at two years in the deflazacort group but the data for the placebo group were not reported.

(e) Acne

The number of participants with acne in treatment and placebo groups was reported in two studies (Griggs 1991; Mendell 1989). Analysis of pooled data from these studies demonstrated a trend to develop acne in the prednisone 0.75 mg/kg/day group after six months of treatment as compared to placebo but this was not statistically significant, with a RR of 1.80 (95% CI 0.97 to 3.36) (*see* Graph - Outcome 13 Acne - prednisone).

Griggs 1991 also compared prednisone 0.3 mg/kg/day with placebo and after six months of treatment there was no significant difference in acne in the prednisone and placebo groups, with a RR of 0.73 (95% CI 0.18 to 3.0) (*see* Graph - Outcome 13 Acne - prednisone).

Mendell 1989 compared prednisone 1.5 mg/kg/day with placebo and after six months of treatment there was a trend to develop acne in the prednisone group, but this was not statistically significant, with a RR of 1.77 (95% CI 0.84 to 3.73) (*see* Graph - Outcome 13 Acne - prednisone).

(f) Osteoporosis, fractures

None of the included studies performed bone densitometry studies. Two studies (Griggs 1991; Mendell 1989) instructed the participants in the study to take 0.3 gm calcium carbonate with each meal. Fractures were commented upon in only one of the included studies (Angelini 1994). Pathological fracture of tibia in one patient in the deflazacort treated group was reported by Angelini 1994. There was no description of the timing of fracture in relation to duration of deflazacort treatment, circumstances leading to the fracture, or results of any bone density studies. One participant in the placebo treatment group in Griggs 1991 dropped out of the study because of an arm fracture and this incident was reported in a subsequent study (Griggs 1993).

(g) Hyperglycemia / glycosuria

Two studies (Angelini 1994; Backman 1995) checked blood glucose and another two (Griggs 1991; Mendell 1989)

checked urine dipstix. Glycosuria was reported in one patient on prednisone 0.75 mg/kg/day by Griggs 1991. The severity of glycosuria and its impact were not reported.

(h) Hypokalemia

Only Angelini 1994 and Backman 1995 performed blood tests for electrolyte surveillance. Angelini 1994 reported "mild hypokalemia" in three of 11 deflazacort-treated participants but this was "easily correctable" with oral potassium supplements.

(i) Hypertension

Hypertension with a blood pressure of 130/110 was reported in one participant taking prednisone 0.75 mg/kg/day by Griggs 1991.

(j) Gastrointestinal side effects

Gastrointestinal side effects were defined differently and inconsistently in the included studies.

Mendell 1989 grouped increased appetite, nausea and stomach discomfort under the umbrella of gastrointestinal symptoms; these, as a whole, were not significantly different between the placebo and prednisone treatment groups. Griggs 1991 reported increased appetite as a separate side effect and this was significantly more frequent in the prednisone 0.75 mg/kg/day group as compared to the placebo ($p = 0.02$). Angelini 1994 reported that in their two-year study, none of the participants developed gastrointestinal disturbances on deflazacort 2 mg/kg on alternate days; they had, however, treated all the children with antacids (drug name not specified). Gastrointestinal side effects were not reported by the parents of the participants in the Backman 1995 study of prednisone 0.35 mg/kg/day.

(k) Cataracts

The patients were evaluated for cataracts in three of the five included studies (Angelini 1994; Griggs 1991; Mendell 1989) but the precise examination (slit lamp or red reflex) performed for detection of cataracts was not described. No cataracts were reported.

(l) Death

Two deaths were reported during the study by Backman 1995. A 16-year-old boy died of pneumonia and a four-year-old died during an appendectomy. The authors did not report whether the deaths occurred during the prednisone or the placebo phase of this crossover study.

(m) Sepsis

Specific monitoring to document episodes of intercurrent infection was described in two studies (Griggs 1991; Mendell 1989). The treatment strategy for exposure to chicken pox (varicella zoster) was not described in any of the included studies. Apart from the 16 year old boy who died of pneumonia, described above (Backman 1995), no other episodes of infection were reported.

Discussion

Thirty-seven studies of glucocorticoid corticosteroids in Duchenne muscular dystrophy over the last three decades were identified. Of these, five were randomised controlled studies which were considered appropriate for analysis according to strict previously defined criteria; four trials studied prednisolone or prednisone against placebo and one studied deflazacort against placebo. The included studies comprised 249 participants, with 88 in the placebo groups and 161 in the glucocorticoid corticosteroid treatment groups. With regard to ambulatory status, 71 of the 88 participants in the control group and 128 of the 161 in the treatment groups were walking, either independently or with the help of long leg braces. The two large studies (Griggs 1991; Mendell 1989) contributed the majority of the patients (202 of 249) to this review. The treatment groups included prednisone (n = 134), prednisolone (n = 10) and deflazacort (n = 17). Unfortunately, the two large studies of deflazacort in DMD (Brooke 1996; Reitter 1995) comprising 206 participants in total have not been published and their data are not available.

Primary outcome measure: prolongation of time to loss of walking

Loss of walking ability is the key milestone in the natural history of DMD and is of maximal functional significance. Prevention or postponement of this event is the key aim of therapeutic interventions in the first decade of life of these patients and is a desired outcome measure. However, this was not the stated primary outcome measure of any of the randomised studies because of the large number of patients and

the duration of a randomised controlled study which would be needed to have the power to demonstrate this effect (Muntoni 2002). As the major contributor to the loss of walking is progressive muscle weakness, measurements of muscle strength have been used as a surrogate marker in clinical trials, which can be completed in as short a time as six months. These short-term studies do not demonstrate the prolongation of time to loss of walking or allow evaluation of adverse effects which develop after long-term use of glucocorticoid corticosteroids.

Mendell 1989, Griggs 1991, Angelini 1994 and Rahman 2001 were six-month-duration short-term studies and not designed to evaluate prolongation of time to loss of walking as an outcome measure of glucocorticoid corticosteroid treatment.

Angelini 1994, in his two-year study of deflazacort 2 mg/kg on alternate days, reported prolongation of walking by 13 months. Four of the 17 boys in the deflazacort group became 'wheelchair bound' at a mean interval of 33.2 months after onset of treatment. Six of the 11 boys in the control group became wheelchair bound at a mean interval of 20.5 months after onset of treatment. The difference of 13 months between these two sets of participants who lost walking ability was reported by the authors as "mean prolongation of walking", ignoring the 13 participants in the deflazacort group and five in the placebo group who were still walking at the end of the study. The age at the end of the study for the boys who remained ambulant was not reported and was not available on contacting the lead investigator. It was therefore not possible to construct Kaplan-Meier survival curves for evaluating prolongation of walking as an outcome measure.

The need for appropriate statistical analysis is further highlighted by some disparities which cannot be explained easily. Deflazacort and placebo groups were evenly matched at randomisation, and for the participants who lost ambulation during the study, the mean age of becoming wheelchair bound was very similar (deflazacort group 108 months, and placebo group 104 months). Comparing the deflazacort and placebo groups, the significance of the difference of 13 months in duration of walking between randomisation and becoming wheelchair bound cannot be ascertained without knowing the ages of the ambulant children at the end of the study.

Secondary outcome measures

Strength

There was statistically significant improvement in various strength and function parameters in the glucocorticoid corticosteroid treatment groups. Muscle strength was measured on MRC-based scores in all five of the included studies and with myometry in two studies (Angelini 1994 and Rahman 2001). Different methodology was used for the muscle strength scores calculated by manual muscle testing on the MRC scale. Mendell 1989, Griggs 1991 and Rahman 2001 reported muscle strength as the average muscle score described in Brooke 1981 and Brooke 1983. This protocol includes manual muscle testing of 34 muscle groups, grouped according to an expanded 10-point scale based on the MRC method. Backman 1995 reported average muscle strength and obtained this by examining 26 muscle groups on the MRC scale, graded from 0 to 5. Performance scores were added and divided by the number of muscle groups to get the average muscle strength. Angelini 1994 reported MRC index based on manual muscle testing of four muscle groups on the six-point MRC scale.

Function

There was evidence of statistically significant improvement in various functional parameters over the short-term in the glucocorticoid corticosteroid treated group. The functional parameters showing improvement included time taken to rise from the floor, time taken to walk nine metres, time taken to climb four stairs and the leg functional grade. It is however important to note that none of the included studies reported any non-ambulant (wheelchair bound) patients to regain the ability to walk on treatment with prednisone.

Data from Griggs 1991; Mendell 1989, and Rahman 2001 demonstrated a statistically significant improvement in time taken to rise to stand in the prednisone/prednisolone treatment groups on all dose regimes (0.3, 0.75 and 1.5 mg/kg/day). The muscle weakness in Duchenne muscular dystrophy leads to increasing

difficulty in rising from the floor at around five years of age. The ability to rise from the floor is lost in the latter part of the first decade of life, and postponement of this milestone as a result of treatment can be used as an outcome measure. These studies, however, were short-term, included non-ambulant patients, and were not designed to be statistically powerful enough to demonstrate a significant difference in this outcome measure.

There was a statistical improvement in the time taken to walk nine metres in all prednisolone treatment groups in three trials (Griggs 1991; Mendell 1989, and Rahman 2001). Leg function grades also showed a statistically significant improvement in all prednisone/prednisolone treatment groups in the same trials.

One of the desired effects of any successful treatment in Duchenne muscular dystrophy is the preservation of respiratory muscle strength, thereby preserving the pulmonary function and postponing or removing the risk of nocturnal hyperventilation and respiratory failure. A good marker of respiratory reserve is the forced vital capacity and this was measured in two of the large included studies (Griggs 1991; Mendell 1989). A statistically significant improvement in the forced vital capacity in all prednisolone treatment groups was present after six months of treatment. Parallel results are available from non-randomised cohort studies (Biggar 2001; Silversides 2003) which showed strength improvement and stabilisation of forced vital capacity over the long term in deflazacort treated patients (see below).

Strength of evidence

Mendell 1989 and Griggs 1991 were the two studies with the largest patient numbers and they both scored highly on the Jadad score. Although the studies had large patient numbers, they were only short-term and studied the effect of glucocorticoid corticosteroids over six months. The study by Backman 1995 was of good quality, but again short-term (six months) and furthermore data were not available. Rahman 2001 scored well on the Jadad score and information provided by the authors indicated adequate allocation concealment but the study had small participant numbers and was short-term (six months). This study was randomised but only the patients were blinded to treatment. Side effects were not described. Angelini 1994 had good Jadad scores. This study tested the effects of alternate day deflazacort over a two-year period. The participant numbers in this study, however, were also small (28) with 17 in the deflazacort treatment group and 11 in the placebo group. Allocation concealment was uncertain in four of the included studies (Angelini 1994; Backman 1995; Griggs 1991; Mendell 1989). The authors of one study (Rahman 2001) provided information indicating adequate allocation concealment. Our review did not identify any systematic bias in the included randomised controlled trials which would affect the results. The effects of treatment appeared consistent across the trials.

Dose response relationship

Pooled data from Griggs 1991; Mendell 1989, and Rahman 2001 demonstrated a statistically significant improvement in muscle strength (reported as muscle strength score) with prednisone/prednisolone treatment over six months. The improvement occurred with all three treatment regimes (0.3 mg/kg/day, 0.75 mg/kg/day and 1.5 mg/kg/day). Clinically, it would be important to use the minimum effective dose of glucocorticoid corticosteroid. To answer this question, the forest plots showing studies grouped by dosage of prednisone/prednisolone were reviewed. The impression is that the benefit increases as dose increases from 0.3 mg/kg/day to 0.75 mg/kg/day, but there is little evidence of an increase in benefit when the dose is further increased from 0.75 to 1.5 mg/kg/day. This suggests that the middle dosage of 0.75 mg/kg/day is adequate to achieve what benefit prednisone can provide. However, this is partly confounded by differences between studies so that such a visual inference must be treated with considerable caution. A proper investigation of the prednisone dose/response relationship to identify the optimum dose would need individual patient data within study analyses. We will attempt to access these data for future revisions of this review. We also recommend that future studies make arrangements for provision of individual patient data for these analyses.

Co-interventions

The co-interventions identified included calcium carbonate given daily in Mendell 1989 and Griggs 1991, antacids given routinely to all patients in Angelini 1994, and dietetic advice to avoid weight gain in Mendell 1989, Griggs 1991 and Angelini 1994. These co-interventions, however, are clinically extremely unlikely to be responsible for the