Cochrane Library

Cochrane Database of Systematic Reviews

Oral steroids for long-term use in cystic fibrosis (Review)

Cheng K, Ashby D, Smyth RL

Cheng K, Ashby D, Smyth RL.
Oral steroids for long-term use in cystic fibrosis.
Cochrane Database of Systematic Reviews 2015, Issue 12. Art. No.: CD000407.
DOI: 10.1002/14651858.CD000407.pub4.

www.cochranelibrary.com

WILEY

TABLE OF CONTENTS

[Intervention Review]

Oral steroids for long-term use in cystic fibrosis

Katharine Cheng[1], Deborah Ashby[2], Rosalind L Smyth[3]

[1]c/o Cochrane CFGD Group, Department of Women's and Children's Health, University of Liverpool, Liverpool, UK. [2]School of Public Health, Imperial College London, London, UK. [3]Institute of Child Health, UCL, London, UK

Contact: Katharine Cheng, kcheng31@its.jnj.com.

Editorial group: Cochrane Cystic Fibrosis and Genetic Disorders Group.
Publication status and date: Stable (no update expected for reasons given in 'What's new'), published in Issue 4, 2021.

Citation: Cheng K, Ashby D, Smyth RL. Oral steroids for long-term use in cystic fibrosis. *Cochrane Database of Systematic Reviews* 2015, Issue 12. Art. No.: CD000407. DOI: 10.1002/14651858.CD000407.pub4.

ABSTRACT

Background

In cystic fibrosis (CF) airway obstruction and recurrent respiratory infection lead to inflammation, long-term lung damage, respiratory failure and death. Anti-inflammatory agents, e.g. oral corticosteroids are used since inflammation occurs early in disease. This is an update of a previously published review.

Objectives

To assess the effectiveness of oral corticosteroids in respiratory complications in CF, particularly lung function and adverse events. We examined long-term use (over 30 days) only.

Search methods

We searched the Cochrane CF and Genetic Disorders Group Trials Register comprising references identified from comprehensive electronic database searches and handsearches of relevant journals and abstract books of conference proceedings.

Most recent search: 28 August 2015.

Selection criteria

Randomised trials comparing oral corticosteroids given for more than 30 days with placebo or no additional therapy in people with CF.

Data collection and analysis

Two authors independently assessed study eligibility and quality.

Main results

Of eleven studies identified, three (354 participants) were included: two with four-year follow up and one with 12-weeks follow up. Data were lacking on predefined outcomes; common outcomes were examined at different time-points and presented differently. Meta-analyses were not possible.

In one study, oral corticosteroids at prednisolone-equivalent dose of 1 mg/kg alternate days slowed progression of lung disease; at two and four years, % predicted FEV_1 in the 1 mg/kg group changed significantly more than in the placebo group ($P < 0.02$). During the first two years, the 2 mg/kg group was not significantly different from the placebo group. Linear growth retardation was observed from six months in the 2 mg/kg alternate days prednisolone group and from 24 months in the 1 mg/kg alternate days prednisolone group.

Adverse events terminated one four-year study early. Year 10 follow up showed catch-up growth started two years after treatment ceased. Alternate-day treatment with oral corticosteroids may have impaired growth until adulthood in boys.

Authors' conclusions

Oral corticosteroids at prednisolone-equivalent dose of 1 to 2 mg/kg alternate days appear to slow progression of lung disease in CF; benefit should be weighed against occurrence of adverse events. Risk-benefit analysis of low-dose alternate days corticosteroids is important. No further trials of this intervention are anticipated, and hence the review will no longer be regularly updated. However, if any new data are published, these will be incorporate when available.

PLAIN LANGUAGE SUMMARY

Use of oral steroids for cystic fibrosis

Cystic fibrosis causes frequent lung infection and the airways become blocked with mucus. This in turn leads to inflammation, which causes more lung damage and more mucus to be produced. Corticosteroids are strong drugs given to treat this inflammation. The review includes three trials; one for 12 weeks and two with four-year follow up. We could not combine any data. Trials showed that oral steroids of 1mg/kg to 2 mg/kg (prednisolone equivalent) given every other day seemed to slow the advance of lung disease. However, there are serious adverse effects such as cataracts and the slowing of growth at the higher dose. These led to one trial stopping early. Follow-up data show that catch-up growth started two years after treatment ceased. Treatment must use the lowest effective dose and the shortest duration of therapy to reduce the risk of a permanent effect on growth. A dose of 1 mg/kg on alternate days might be considered for up to 24 months, but close attention should be paid to adverse effects. We do not expect any further trials of this treatment to be undertaken, so we do not plan to continue to regularly update the review. However, if any new information is published, we will include this when it is available. This is an update of a previously published review.

BACKGROUND

Description of the condition

The defective cystic fibrosis (CF) gene is responsible for causing an abnormal airway surface environment, which leads to both airway obstruction by mucus plugging and recurrent respiratory infection. This leads to inflammation and eventually long-term lung damage (bronchiectasis), respiratory failure and death. The persistent presence of pathogenic organisms, including *Staphylococcus aureus*, *Haemophilus influenza*, and *Pseudomonas aeruginosa* in the airways is associated with a powerful inflammatory response which is ineffective in clearing the organisms from the lungs (Balfour-Lynn 1996).

It has been recognised that the inflammatory process itself may contribute to lung injury (Konstan 1996). The most characteristic feature of lung inflammation in CF is the influx of huge numbers of white cells, called neutrophils, into the airways (Konstan 1993). These numerous neutrophils break down and release a number of substances, including deoxyribonucleic acid (DNA), which makes the sputum thick and sticky. They also release products which cause direct lung damage. These include oxygen metabolites (oxidants) and elastase, which damages the airway wall and increases mucus secretion, therefore aggravating airway obstruction. Elastase also causes the secretion of a substance called IL-8, a type of cytokine, which attracts more neutrophils into the airways.

Bronchoscopy combined with bronchoalveolar lavage (BAL), a technique of examining the airways and getting information about the composition of airway fluids, have helped further understanding of inflammation and lung injury in CF. The inflammatory process occurs early in life, a recent study showing showed that lung inflammation can occur in CF infants as young as four weeks (Khan 1995). Another study showed that even infants without clinically obvious lung disease still had evidence of airway infection with inflammation predominated by neutrophils (Armstrong 1995). Studies have also shown that the inflammatory response is also detectable in the airways of people with clinically mild disease (Konstan 1994). BAL in people with CF with mild lung disease has been shown to contain large numbers of inflammatory cells, including neutrophils and free elastase (Konstan 1994).

How the intervention might work

Current evidence suggests that inflammation in CF occurs early in life and may contribute to lung damage. This is the rationale for the use of anti-inflammatory therapy in CF. Corticosteroids are powerful anti-inflammatory agents which have been used widely in a number of diseases for several decades and have several important effects on neutrophils, such as stopping the neutrophils converting to their active state (Schleimer 1990) and stopping them producing digestive enzymes (Llewellyn-Jones 1994).

Why it is important to do this review

This review aims to determine whether there is clear evidence that one anti-inflammatory treatment, oral corticosteroids, is beneficial in the treatment of lung disease in people with CF. However, the use of corticosteroids is also associated with well-known, significant side effects. Use of high doses, particularly over a prolonged period of time is associated with changes in appearance including a 'moon-face', weight gain, centripetal redistribution of fat, muscle wasting, acne, bruising, thinning of the skin and stretch marks. High doses can also precipitate or exacerbate existing diabetes mellitus. Prolonged use is associated with osteoporosis (thinning of the bones) and cataract formation. Corticosteroids also increase the risk of contracting certain types of infection and reduce the capacity of the body to respond to serious infection. In children, one of the most worrying side effects is suppression of growth.

This is an update of a previously published review (Cheng 1999; Cheng 2011; Cheng 2013).

OBJECTIVES

The objective of this review is to determine the effectiveness of oral corticosteroids in the management of CF. We wished to test the hypotheses that oral corticosteroids:

1. reduce the number of days of intravenous antibiotics for respiratory exacerbations;
2. reduce the need for hospital admission for respiratory exacerbations;
3. improve or prevent the decline in objective tests of lung function (forced expiratory volume in one second (FEV_1); forced vital capacity (FVC); and forced expiratory flow 25-75% (FEF_{25-75}));
4. improve exercise tolerance;
5. improve nutritional status;
6. are associated with adverse effects including changes in appearance including Cushingoid appearance, growth suppression, diabetes mellitus, cataracts, osteoporosis and opportunistic infection;
7. improve quality of life;
8. improve survival.

We intended to assess the above hypotheses for long-term anti-inflammatory use only.

METHODS

Criteria for considering studies for this review

Types of studies

Randomised controlled trials, published and unpublished.

Types of participants

Children and adults, of any age, with defined CF diagnosed clinically and by sweat or genetic testing. People with CF at all stages of lung disease were included.

Types of interventions

Where oral corticosteroids have been compared to placebo or existing conventional therapy for at least 30 days.

Types of outcome measures

Primary outcomes

1. Objective lung function tests
   a. forced expiratory volume at one second (FEV_1), forced vital capacity (FVC), forced expiratory flow from 25% to 75% of vital capacity (FEF_{25-75}) (% predicted) absolute change from baseline

b. FEV_1, FVC, FEF_{25-75} (% predicted) post-treatment

2. Number of days of intravenous antibiotics for respiratory exacerbations
3. Hospitalisation rates for respiratory exacerbations

Secondary outcomes

1. Objective change in exercise tolerance as measured by a maximal exercise test, including a 12-minute walk if this had been measured
2. Change in growth and nutritional indices expressed as change in z scores for height and weight, change in body mass index, percentage weight for height and height and weight centiles. As increase in weight or percentage ideal body weight for height might occur at the expense of reduced growth velocity, we wished to consider these in the context of change in height. Z score is a measure of nutritional status, where weight is expressed as a percentage of ideal for height and then compared to the standard for the population (Frisancho 1990).
3. Occurrence of adverse effects such as changes in appearance including Cushingoid appearance, growth impairment as measured by change in z score for height, cataracts, osteoporosis, obesity, diabetes mellitus requiring regular treatment, occurrence of opportunistic infection categorised as mild (e.g. oral or vaginal thrush, ringworm) or serious (e.g. shingles, herpes virus, life-threatening infection). Other adverse effects if noted were also assessed. If data were available, we planned to assess bone mineral density z score as a continuous variable.
4. Quality of life
5. Survival or age at death

Search methods for identification of studies

Electronic searches

Relevant studies were identified from the Group's Cystic Fibrosis Trials Register using the terms: anti-inflammatory AND oral AND steroid.

The Cystic Fibrosis Trials Register is compiled from electronic searches of the Cochrane Central Register of Controlled Trials (CENTRAL) (updated each new issue of *The Cochrane Library*), weekly searches of MEDLINE, a search of Embase to 1995 and the prospective handsearching of two journals - *Pediatric Pulmonology* and the *Journal of Cystic Fibrosis*. Unpublished work is identified by searching the abstract books of three major cystic fibrosis conferences: the International Cystic Fibrosis Conference; the European Cystic Fibrosis Conference and the North American Cystic Fibrosis Conference. Additional references were found from reference lists. For full details of all searching activities for the register, please see the relevant sections of the Cystic Fibrosis and Genetic Disorders Group Module.

Date of the most recent search of the Group's Cystic Fibrosis Trials Register: 28 August 2015.

Searching other resources

Full text searching of the *Journal of Pediatrics* was also undertaken from the years 1948 to 1997.

Data collection and analysis

Selection of studies

We (KC and RS) independently applied inclusion criteria to all potential reports.

Data extraction and management

We independently attempted to extract data from each randomised controlled trial (RCT) from text, tables and figures. For continuous outcomes, we intended to record either mean absolute change from baseline for each group or mean post-treatment or intervention values and standard deviation or standard error for each group.

We planned to group outcome data into those measured at one, three, six, twelve months and annually thereafter. However, outcome data were recorded at other time periods and reported within this review. For future updates, if outcome data are recorded at other time periods then consideration will be given to examining these as well.

Assessment of risk of bias in included studies

In order to assess the risk of bias in the included studies, we followed the guidance given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2009). We considered such aspects as generation of randomisation sequence and allocation concealment. If we regarded these as adequately performed, then there was a low risk of bias to the study; if we regarded these as inadequately performed, then there was a high risk of bias to the study; and if they were considered unclear then the risk of bias was unclear too. We also considered the degree of blinding and the risk of bias increased as the number of people blinded to the intervention decreased. Finally, we considered whether issues resulting from incomplete outcome data were adequately addressed and whether this led to a low, high or uncertain risk of bias.

Measures of treatment effect

We aimed to calculate a pooled estimate of the treatment effect for each outcome across studies. For binary outcomes, we planned to express this as a pooled odds ratio (OR) (the odds of an outcome among treatment allocated participants to the corresponding odds among controls) and for continuous outcomes, we would express a pooled estimate of the treatment effect by calculating the mean difference (MD).

The data from these studies are essentially longitudinal in nature. The extractions below are the best that can be hoped for given the constraints of extracting summaries from published reports, although we recognise there are potentially issues of multiple end points. We would require individual patient data for a fuller analysis, but the merits of making the necessary investment are best judged after reviewing the available studies on the basis of reports.

Unit of analysis issues

We did not include any cross-over studies; we do not plan to include any cross-over studies in the future as we feel these are not appropriate to this intervention.

Dealing with missing data

Where sufficient data were not available in the published reports or in the abstract from the conference proceedings, we attempted to contact first and last authors of the studies to obtain individual or summary data.

In order to allow an intention-to-treat analysis, we planned to collect data on the number of participants with each outcome event, by allocated treated group, irrespective of compliance and whether or not the participant was later thought to be ineligible or otherwise excluded from treatment or follow up.

Assessment of heterogeneity

We intended to test for heterogeneity between study results using a standard chi squared test and the I^2 statistic (Higgins 2003). We planned to grade the degrees of heterogeneity using the I^2 values as follows: low (0% to 40%), moderate (30% to 60%), substantial (50% to 90%) and considerable (75% to 100%).

Data synthesis

We have analysed the data using a fixed-effect model. If, in future updates of this review, we identify substantial or considerable heterogeneity, we will consider analysing the data using a random-effects model.

Subgroup analysis and investigation of heterogeneity

For future updates, if there are sufficient numbers of studies we will explore the following sources of heterogeneity:

1. age of participants;
2. interaction with other drugs.

Sensitivity analysis

We will also examine the robustness of our results using a sensitivity analysis including and excluding studies with a high risk of bias.

RESULTS

Description of studies

Results of the search

Eleven studies were identified by the searches. Three studies met the inclusion criteria (Auerbach 1985; Eigen 1995; Greally 1994); four studies were excluded (Cohen-Cymberknoh 2008; Dovey 2007; Linnane 2001; Pantin 1986); and four studies are listed as awaiting classification (we do not currently have sufficient details to assess whether these studies are eligible for inclusion in our review and have contacted the authors of the study for more information) (Kapustina 2008; Nyamugunduru 1998; Pukhalsky 2007; Pukhalsky 2008).

Included studies

Summary details are given in the Characteristics of included studies tables, including the time points reported in the primary studies.

Seven studies were identified by the searches, of which three, with a total of 354 participants, met the inclusion criteria.

Participants

The ages of the participants ranged from 1 year to 19.5 years. In one study, the participants were stated as having mild to moderate lung disease, but an objective measure of lung disease, such as mean per cent predicted FEV_1, was not reported (Auerbach 1985). In the other two studies the upper or lower limits of severity of lung disease were stated as FEV_1 less than 85% predicted in one (Greally 1994); and as FEV_1 greater than 60% predicted in the other (Eigen 1995).

Interventions

Two studies examined alternate-day corticosteroids (Auerbach 1985; Eigen 1995), in the third study corticosteroids were given daily for the first two weeks and then on alternate days for 10 weeks (Greally 1994). In each study the comparison of treatment was with placebo and in one study two doses were compared with placebo (Eigen 1995). The dose of prednisolone varied from 1mg/kg day on alternate days (Eigen 1995) to 2 mg/kg on alternate days (Auerbach 1985; Eigen 1995) to 2 mg/kg daily for 14 days followed by 1 mg/kg on alternate days for 10 weeks (Greally 1994).

The duration of administration of oral corticosteroids and follow up ranged from 12 weeks (Greally 1994) to four years (Auerbach 1985; Eigen 1995). Although not strictly a 'short-term' study (less than 30 days), the study by Greally was a short-term one in comparison to the other two studies (Greally 1994). It was also primarily explanatory rather than pragmatic; its aim was to explore the biological mechanisms of oral corticosteroids, rather than to give treatment recommendations (Murray 1991). The authors had previously demonstrated higher serum concentration of interleukin-1alpha and interleukin-2R in participants with CF compared to controls; and in this study aimed to investigate the effect of oral prednisolone on these interleukins and also immunoglobulin G (IgG). In one of the long-term studies no intermediate outcome data were presented between baseline and four years (Auerbach 1985).

Outcome measures

Four outcomes, which we had intended to assess, had not been reported in any of the three RCTs. These were exercise tolerance, number of days of intravenous antibiotics for respiratory exacerbations, quality of life and survival. The two outcomes common to all three studies were lung function and adverse events.

However, data on the lung function primary endpoint were presented in different ways in each study. In the study by Greally, lung function was expressed as mean absolute change in per cent predicted FEV_1 at 14 days and 12 weeks, with confidence levels for the change quoted (Greally 1994). In the Auerbach study the mean absolute level of per cent predicted FEV_1 at baseline and four years were reported, together with standard error (Auerbach 1985). In the third study graphs of mean change from baseline of FEV_1 and FVC were shown but no standard errors or standard deviations were reported (Eigen 1995).

The adverse events reported were not the same in each study. The Greally study specifically sought the adverse events of raised blood pressure, high blood sodium, low blood potassium, fluid retention and blood glucose abnormalities (Greally 1994). The Auerbach study regularly measured height and weight of participants, but other adverse effects did not seem to have been

systematically sought (Auerbach 1985). The Eigen study monitored adverse events at each clinic visit, i.e. three-monthly, specifically looking for raised blood glucose levels, cataracts, liver enzyme abnormalities, or chest infections with unusual organisms (Eigen 1995). In the Effects of interventions section of this review, the adverse events are described as they have been reported in the published reports. None of the studies reported whether or not Cushingoid appearance or osteoporosis had developed. Two of the three studies reported effect on height (Auerbach 1985; Eigen 1995); although, as the other study was comparatively short, there would not have been sufficient time for an effect on height to have occurred (Greally 1994). Two of the three studies reported the development of diabetes or glucose intolerance (Eigen 1995; Greally 1994). Two studies evaluating different groups of participants reported the development of cataracts; one was a four-year follow-up study (Eigen 1995) and the other a 10-year follow up of some of the participants in another four-year study (Auerbach 1985). Only one study reported the development of opportunistic infection (Greally 1994).

In the study by Eigen, due to an excess of adverse events, the high dose prednisolone (2 mg/kg on alternate days) group was discontinued prematurely three years after accrual of participants commenced and the low dose (1mg/kg on alternate days) was also discontinued a year later (Eigen 1995). All three treatment groups were analysed using a repeated measures ANOVA for the first 24 months, but a second analysis was done comparing the 1 mg/kg prednisolone group with placebo for 48 months. Participants, who were in the 2 mg/kg on alternate days group, were not included in the latter analysis because some participants in this group had not received the study drug for as long as 24 months. For either treatment group it was not clear from the report exactly how long oral corticosteroids were given, but it appears to have been a variable length of time, depending on when enrolment into the study took place.

Excluded studies

Four studies were excluded from the review: one study was not randomised (Pantin 1986) and another study did not meet our inclusion criteria as the steroids were not given to treat an exacerbation (Linnane 2001). The third study was excluded as treatment duration was less than 30 days (Dovey 2007) and the remaining study was excluded as the steroids were given to treat allergic bronchopulmonary aspergillosis and not as part of the general anti-inflammatory management of CF (Cohen-Cymberknoh 2008).

Risk of bias in included studies

Allocation

Generation of the randomisation sequence, and also the risk of bias due to this, was unclear in two studies (Auerbach 1985; Greally 1994). We judged the generation of randomisation sequence to be adequate and estimated the risk of bias from this as low in the third study, which used a computer-generated random number sequence in blocks of six (Eigen 1995).

Concealment of allocation was unclear in all three included studies and we deemed these to have an unclear risk of bias (Auerbach 1985; Eigen 1995; Greally 1994).

Blinding

Double blinding was reported specifically in all three studies (Auerbach 1985; Eigen 1995; Greally 1994). However, the authors acknowledge that double-blinding might not have been possible. At the doses used, it would have been obvious from the somatic changes resulting from the use of corticosteroids, which participants were in the treatment group. We therefore judged all three studies to have an unclear risk of bias due to blinding (Auerbach 1985; Eigen 1995; Greally 1994).

Incomplete outcome data

Analysis was done on an intention-to-treat basis in two studies and this led us to estimate a low risk of bias for these studies (Eigen 1995; Greally 1994). In the third study, 45 participants were initially randomised, but 11 did not complete the study (reasons were given) (Auerbach 1985). It was unclear whether these 11 withdrawals had been included in the analysis. We therefore judged this study to have an unclear risk of bias (Auerbach 1985).

Effects of interventions

Due to the variations in presentation of data and the different time points at which outcomes were examined, no aggregation of data was possible. We have been unsuccessful so far in obtaining raw data from two of the studies; however, we have received the data from the remaining study (Greally 1994). We have not been able to contact any of the authors of the study by Auerbach (Auerbach 1985), but have been assured by the authors of the study by Eigen that they will send us their raw data (Eigen 1995). For this review we have summarised the data as presented in the published reports. Hence we currently report P values, rather than actual group data, with the results of each outcome as a mean for each group or percentages together with confidence intervals (CIs). However, with the exception of the study by Greally, this has not been possible because the data were not expressed in this way in the published reports (Greally 1994). The authors acknowledge that the reader will have difficulty in assessing whether a statistically significant change is also clinically important.

Primary outcomes

1. Objective lung function tests

All studies showed some improvement or delay in decline in lung function in the oral steroid-treated groups compared with placebo.

a. FEV_1/FVC/FEF_{25-75} (% predicted) absolute change from baseline

Greally examined lung function at relatively short time points, 14 days and 12 weeks (Greally 1994). Mean absolute change in percent predicted FEV_1 with the 95% CI for the difference between groups were reported at 14 days and 12 weeks. The mean absolute change in percent predicted FEV_1 at 14 days was 7.7% in the treatment group compared to -1.0% in the placebo group (95% CI for the difference between groups 15.08 to 2.32) and at 12 weeks was 6.3% in the prednisolone group compared to -1.8% in the placebo group (95% CI 15.75 to 0.45). The improvement observed in the treatment group is likely to be perceived as beneficial by the participant. We assumed that the standard deviation for both treatment and control groups was the same and, using the formulae for calculating the standard error of the difference between two means and the confidence interval of the difference between two means,

calculated the standard deviations of the two groups. Data on FEV_1 and FVC have been entered into the data tables.

Auerbach reported that at four years the mean per cent predicted FEV_1 was significantly higher in the prednisolone group at a dose of 2 mg/kg on alternate days (103%) compared to the placebo group (87%), P < 0.005. At baseline both groups had similar mean per cent predicted FEV_1 (Auerbach 1985).

In the study by Eigen, an excess of adverse events resulted in the high dose prednisolone (2 mg/kg on alternate days) being discontinued prematurely three years after accrual of participants commenced and the low dose was also discontinued a year later (Eigen 1995). All three treatment groups were analysed using a repeated measures ANOVA for the first 24 months but a second analysis was done comparing the 1 mg/kg on alternate days prednisolone group with placebo for 48 months. Actual group data were not reported.

Actual group data for FEV_1 and FVC were not reported. With regards to FVC, when the three groups were compared for the initial 24 months, the mean change in per cent predicted FVC was higher in the 1 mg/kg group than the placebo group at all six-monthly time points (P < 0.0001); and at all time points the mean change in per cent predicted FVC was greater in the 2 mg/kg group than the placebo group (P < 0.01). When the 1 mg/kg prednisolone group and the placebo group were compared for the first 48 months of the study, the steroid treated group had a greater change in per cent predicted FVC, which was sustained throughout the period (P < 0.0025). At 24 months, 70.4% participants treated with 1 mg/kg prednisolone had an increase in per cent predicted FVC, compared with 54.9% participants treated with 2 mg/kg prednisolone and 41.6% participants treated with placebo. With regards to FEV_1, during the first 24 months, the 1 mg/kg prednisolone group had a significantly greater change from baseline in per cent predicted FEV_1 than placebo. There was no significant difference between the 2 mg/kg group and the placebo group. When the 1 mg/kg prednisolone group were compared for the full 48 months of the study, the prednisolone treated group had a better change from baseline in mean per cent predicted FEV_1 than the placebo group (P < 0.02), in that there was a decline in mean per cent predicted FEV_1 in the placebo group from 79.2% at baseline to 73.4% at 48%, but no decline in the prednisolone treated group.

2. Number of days of intravenous antibiotics for respiratory exacerbations

This outcome was not reported in any of the four studies.

3. Hospitalisation rates for respiratory exacerbations

Eigen reported that the hospitalisation rates were similar in the three comparison groups: 52% in the 1 mg/kg group; 59% in the 2 mg/kg group; and 59% in the placebo group (Eigen 1995). It was also noted that hospitalisations per participant were similar in the three groups: 1.73 in the 1 mg/kg group; 1.82 in the 2 mg/ kg group; and 1.86 in the placebo group. The periods during which these hospitalisations per participant were calculated is not clear from the report.

Auerbach reported that five (24%) of the prednisolone-treated participants were admitted to hospital nine times during 846 patient-months at risk and 10 (42%) placebo-treated participants were admitted 35 times during 941 patient-months at risk (Auerbach 1985).

Greally did not report hospital admissions (Greally 1994).

Secondary outcomes

1. Exercise tolerance

None of the four studies reported this outcome.

2. Growth and nutrition

Height

Height was reported in two studies but presented differently, as mean height and weight in one study (Auerbach 1985) and as height z scores in the other (Eigen 1995).

Auerbach demonstrated that the mean height of the prednisolone group, (2 mg/kg on alternate days) was higher at four years than the placebo group (Auerbach 1985). In the publication the P value was stated as P < 0.025, but the actual changes in each group were not reported. However, long-term follow-up data of this study did suggest an adverse effect on linear growth. In the Auerbach study, Donati suggested in the 10-year follow-up data of 30 out of the 34 participants that there was substantial impairment in growth in the participants who received corticosteroids for four years or more (Donati 1990). Of the 14 participants who were in the original steroid group, nine took corticosteroids for an average (SD) of 9.5 years (1.2 years) and had a mean z score at 10 years of -1.86 (95% CI -2.44 to -1.28), and the five who stopped taking corticosteroids for 4.5 years (0.46 years) had a mean z score of -1.34 (95% CI -2.58 to -0.10). In contrast, of the 16 participants in the placebo group, five never received corticosteroids and five received corticosteroids for 0.6 years (0.3 years) and had a mean z score of -0.70 (95% CI -1.3 to -0.10). The figures for the means and standard deviations were reported in the original paper (*see* Table 1), the 95% CIs have been calculated from these figures. The authors of this review acknowledge that this was an incomplete follow-up study and that although one of the 30 participants died; we do not know why data on the other three were unavailable.

Eigen also showed that treatment with prednisolone adversely affected growth (Eigen 1995). Evidence of this was apparent six months from starting the study in the 2 mg/kg prednisolone group, but not until 24 months in the 1 mg/kg prednisolone group. Linear growth retardation, as defined in this study by a decrease of one z score, occurred statistically significantly more often in the steroid-treated participants at either dose, than those treated with placebo (P < 0.05) in the 1 mg prednisone group OR 2.58 (95% CI 1.18 to 5.63); and for the 2 mg prednisone group OR 3.70 (95% CI 1.73 to 7.92) (Analysis 1.3).

Following six months of treatment and after 12, 18 and 24 months, the high-dose group had a significantly greater reduction in height z score than the placebo-treated group (P < 0.001). For the 1 mg/kg group the height z score was significantly lower than that of the placebo group after 24 months of treatment and also at 36 and 48 months (P < 0.001). Confidence intervals or standard errors were not reported. At 24 months the mean change in height z score was 0.02% for the placebo group, -0.1% for the 1 mg/kg prednisolone group and -0.3% for the 2 mg/kg prednisolone group; at 36 months -0.01% for the placebo group, -0.25% for the 1 mg/kg group; and at

48 months -0.05% for the placebo group and -0.5% for the 1 mg/kg group. These values were read off a graph in the published report.

Lai evaluated long-term growth in 224 of the 243 children enrolled in the Eigen study (Lai 1999). Growth patterns were examined six to seven years after prednisolone was discontinued. At this stage (in 1997) 68% of the participants were 18 years or older. Height z scores among prednisolone-treated participants declined from baseline to three to four years in both genders. Catch-up growth began two years after prednisolone was discontinued.

Among the boys, the z scores for height remained significantly lower after 10 years in those who received prednisolone than in those who received placebo (P = 0. 03). The mean height for boys aged 18 years or older was significantly lower (by 13 percentile points) in the boys who received low-dose prednisolone (P = 0.03); in the 1mg prednisone group, MD -3.90 (95% CI -7.77 to -0.03) and the 2mg prednisone group, MD -4.10 (95% CI -7.82 to -0.38) (Analysis 1.4). The impact of growth suppression was more pronounced and final adult height was affected if the prednisolone was started before puberty. In girls there was no significant difference in height after 18 years of age in those who received prednisolone compared to those who received placebo (P = 0.87); in the 1 mg prednisone group MD -1.00 (95% CI -4.54 to 2.54) and for the 2 mg prednisone group MD -0.50 (95% CI -4.43 to 3.43) (Analysis 1.5). Among the girls, no significant differences in z scores for height were found among prednisolone groups after six years (P = 0.26). In addition, girls who started taking prednisolone at younger ages did not have greater declines in z scores for height than girls who started at older ages. In the follow up of the Eigen study, Lai did not state whether formal tests of interaction were undertaken (Lai 1999).

Weight

All three studies presented data on weight (Auerbach 1985; Eigen 1995; Greally 1994). However, only data from two studies could be entered in the analysis; one study presented data for change in weight (Greally 1994) and the remaining study presented weight in kg (Eigen 1995).

Auerbach demonstrated that the mean height and weight of the prednisolone group, (2 mg/kg on alternate days) was higher at four years than the placebo group (Auerbach 1985). In the publication the P values were stated as P < 0.025 for height and P < 0.005 for weight, but the actual changes in each group were not reported.

Greally reported the change in weight from baseline; weight gain was higher in the oral steroid group, but the result was not significant, MD 0.34 (95% CI -2.32 to 3.00) (Greally 1994) (Analysis 1.6).

Eigen presented absolute values for weight at over 18 years of age split for males and females. For the boys, weight was higher in both treatment groups compared to placebo; this was not statistically significant in the 1mg prednisone group MD -4.60 (95% CI -9.69 to 0.49), but was statistically significant in the 2 mg prednisone group MD -6.70 (95 % CI -11.59 to -1.81]) (Analysis 1.7). For the girls, weight was higher in the 1 mg prednisone group compared to placebo, MD -2.30 (95% CI -6.74 to 2.14); but lower in the 2 mg prednisone group compared to placebo, MD 1.70 (95% CI -3.37 to 6.77) (Analysis 1.8). Neither result was statistically significant for the girls.

Obesity was not reported in any of the studies.

3. Occurrence of adverse effects

(e.g. changes in appearance including Cushingoid appearance, cataracts, osteoporosis, obesity, diabetes mellitus requiring regular treatment, occurrence of opportunistic infection categorised as mild (e.g. oral or vaginal thrush, ringworm) or serious (e.g. shingles, herpes virus, life-threatening infection))

We described earlier which of these adverse events were systematically sought during the course of the studies and have described the occurrence of these outcomes as they were reported in the published reports. As stated in the 'Description of studies' section, 95% CIs were not reported. The study by Auerbach was not analysed on an 'intention-to-treat' basis and there was further loss to follow up at 10 years (Auerbach 1985). Therefore, it was not possible to calculate percentages or rates for any adverse effects. Eigen reported adverse events, but it is not possible to differentiate whether more than one event occurred in the same participant, so again it is not possible to report percentages or rates (Eigen 1995).

The development of a Cushingoid appearance was reported in one study and occurred in four of the prednisolone-treated participants (2 mg/kg on alternate days) (Auerbach 1985).

Development of cataracts was reported in two studies. The 10-year follow-up report of the Auerbach study by Donati reported that two participants had developed cataracts (Donati 1990). Eigen reported that during the first 24 months, cataracts were seen more often in participants in the 2 mg/kg prednisolone group (11 participants) compared to the 1 mg/kg group (three participants) (Eigen 1995). We also noted that seven participants in the placebo group developed cataracts.

Osteoporosis was not specifically noted, but in the follow up to the Auerbach study, Donati reported that two of the prednisolone-treated participants (2mg/kg on alternate days) developed multiple bone fractures (Donati 1990).

Diabetes mellitus requiring regular treatment was not specifically reported in any of the four studies but all four noted varying degrees of glucose intolerance. In the short-term study, Greally reported that one participant developed hyperglycaemia (17 mmol/L) at the end of two weeks of 2 mg/kg prednisolone which settled on the alternate-day regimen (Greally 1994). In the follow up to the Auerbach study, Donati reported that glucose intolerance occurred in 2 of the 14 prednisolone-treated participants (2 mg/kg on alternate days) in whom data were available (Donati 1990). Eigen noted that abnormalities in glucose metabolism (elevated haemoglobin A1c, raised fasting blood glucose concentration or glucose in the urine) were seen more often in the prednisolone 2 mg/kg group than in the 1 mg/kg group (P < 0.05) but there was no difference between the 1 mg/kg and placebo groups (P < 0.05) (Eigen 1995).

Interestingly, occurrence of opportunistic infection was reported only in the shorter-term study (Greally 1994). No opportunistic infections occurred in the treated group but it was not reported whether any occurred in the control group.

4. Quality of life

This was not specifically reported in any of the three studies.

5. Survival or age at death

This was not reported in any of the three studies.

Although not a specific outcome, Auerbach reported that during four years of the study, one participant from the placebo group and none from the prednisolone group died (Auerbach 1985).

DISCUSSION

Oral corticosteroids at a dose of 1 mg/kg to 2 mg/kg (prednisolone equivalent) administered on alternate days over 12 weeks to 4 years appeared to slow the progression of lung disease in CF as supported by FEV_1 and FVC values documented longitudinally. However, in the long term this benefit needs to be weighed against the occurrence of adverse effects (glucose abnormalities, cataracts and growth retardation), especially linear growth suppression. At the higher dose of 2 mg/kg on alternate days, the occurrence of adverse events resulted in early termination of one study by a data safety monitoring committee, outweighing any beneficial effects on lung function (Eigen 1995). The number of days participants had been taking the dose of 2 mg/kg on alternate days was not stated in the published report. Accrual of participants took place between April 1986 and December 1987. Termination of the high dose was in August 1990. Although adverse events were not reported in the other study which used this dose, this may be due to the smaller sample size used (Auerbach 1985). It was disappointing that the contrasting results of the two studies using the higher dose, 2 mg/kg on alternate days, could not be aggregated because of differing presentation of data and the lack of any interim data between baseline and four years in one of these studies. We have attempted unsuccessfully to obtain the raw data from these two studies. Even at the lower dose of 1 mg/kg on alternate days, recommendations to terminate the study prematurely were made, due to the occurrence of adverse effects (glucose abnormalities, cataracts and growth retardation) (Eigen 1995). Long-term follow up of the Eigen study has shown that the height deficit in boys persisted six to seven years after discontinuation of prolonged alternate-day treatment with prednisolone (Lai 2000). It is likely that the shorter adult height was due partly to the effect of long-term treatment with prednisolone and not just the underlying CF. This difference was not seen in girls. These long-term data suggest that when oral corticosteroids are used in people with CF, treatment regimens need to be adjusted to find the lowest effective dose and the shortest duration of therapy in order to minimise the risk of permanent growth impairment, especially in boys. It is very important that the benefits in improved lung function are weighed against the risk to long-term growth.

Although the shorter-term study was primarily explanatory, examining the biological effects of corticosteroids on inflammatory markers, lung function was also assessed and showed an improvement in FEV_1 at both 14 days and 12 weeks, but in this relatively short time period no adverse effects occurred (Greally 1994).

It is disappointing that effects on survival and quality of life measures were not assessed. The development of Cushingoid appearance was reported in only one study (Auerbach 1985). This is a particularly important outcome to people with CF as the resulting effect on quality of life might not compensate for any improvement in breathlessness.

Although we have not been able to perform a formal meta-analysis for any outcome at any time-point, this review has summarised the best information currently available. It is important to note that of the three studies included in this review only one was assessed to be of good quality (Eigen 1995). Information to fully assess the quality of the other two studies was not available (Auerbach 1985; Greally 1994). We have been unable to contact any of the authors of the Auerbach study (Auerbach 1985), but we have been assured that the data from the Eigen study (Eigen 1995), currently on a data tape will be sent to us in due course. We hope to include a quantitative analysis in a future update of this review.

We have identified three abstracts presented at conferences relating to the same RCT by Nyamugunduru (Nyamugunduru 1998). To our knowledge, this is not yet published. The RCT seems to be eligible for inclusion in the review; however, the information in the abstract is insufficient for assessing methodological quality. The lung function data are not presented in a format which can be aggregated with existing included data. We have written again to the authors for further information.

AUTHORS' CONCLUSIONS

Implications for practice

Current evidence suggests that oral corticosteroids at a prednisolone equivalent dose of 2 mg/kg on alternate days is effective but should not be used due to the high risk of occurrence of important side effects. A dose of 1 mg/kg on alternate days might be considered for up to 24 months but close attention to the occurrence of adverse effects is warranted.

Implications for research

Although oral corticosteroids at a dose of 1 mg/kg to 2 mg/kg on alternate days appear to slow the progression of lung disease in CF, this is at the expense of the occurrence of adverse events. The evidence from Eigen's study suggests that growth retardation may appear after 24 months of treatment with prednisolone at 1 mg/kg on alternate days and as early as six months with a dose of 2 mg/kg on alternate days (Eigen 1995). Therefore, further RCTs examining the effectiveness and safety of treatment on a long-term basis are not warranted. However, a survival analysis from the 10-year follow-up study (Auerbach 1985) or indeed from the other long-term study (Eigen 1995) would be helpful in determining whether the use of oral corticosteroids has any effect on long-term survival. It would seem prudent to address the effectiveness of alternative anti-inflammatory agents in future RCTs.

We recommend that any future studies should adequately consider adverse effects particularly quality of life measures to assess acceptability to participants. We would urge trialists to recognise that the results of individual RCTs are likely to be included in systematic reviews such as this. They should therefore consider standardising the presentation of outcomes to enable the data to be aggregated. However, despite these recommendations, we do not anticipate any further trials of this intervention, and hence we do not plan to update the review on a regular basis. If we become aware that any new data have been published, we will incorporate these into the review.

ACKNOWLEDGEMENTS

This review was conducted as an activity of The Cochrane CF and Genetic Disorders Group, supported by grants from the NHS Executive, North West Regional Office, Research and Development Directorate and The Cystic Fibrosis Trust. However, these two organisations are not responsible for the contents of this review.

REFERENCES

References to studies included in this review

Auerbach 1985 *{published and unpublished data}*

* Auerbach HS, Williams M, Kirkpatrick JA, Colten HR. Alternate-day prednisone reduces morbidity and improves pulmonary function in cystic fibrosis. *Lancet* 1985;**2**(8457):686-8.

Donati MA, Haver K, Gerson W, Klein M, McLaughlin FJ, Wohl MEB. Long-term alternate day prednisone therapy in cystic fibrosis [abstract]. *Pediatric Pulmonology* 1990;**9 (Suppl 5)**:322.

Eigen 1995 *{published and unpublished data}*

* Eigen H, Rosenstein BJ, Fitzsimmons S, Schidlow DV, and The Cystic Fibrosis Foundation Prednisone Trial Group. A multicenter study of alternate-day prednisone therapy in patients with cystic fibrosis. *Journal of Pediatrics* 1995;**126**(4):515-23.

Hsu J, Kuhns LR. Longitudinal study in bone absorptiometry in children with cystic fibrosis enrolled in steroid study [abstract]. *Pediatric Pulmonology* 1991;**Suppl 6**:324.

Lai HC, FitzSimmons SC, Allen DB, Kosorok MR, Rosenstein BJ, Campbell PW, et al. Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis. *New England Journal of Medicine* 2000;**342**(12):851-9.

Lai HC, Kosorok MR, Allen DB, FitzSimmons SC, Rosenstein BJ, Campbell PW, et al. Long-term growth evaluation in children with cystic fibrosis with history of regular use of alternate-day prednisone therapy [abstract]. *Pediatric Pulmonology* 1999;**28 (Suppl 19)**:297.

Rosenstein BJ, Eigen H. Risks of alternate-day prednisone in patients with cystic fibrosis. *Pediatrics* 1991;**87**(2):245-6.

Greally 1994 *{published data only}*

* Greally P, Hussain PJ, Vergani D, Price JF. Interleukin-1alpha, soluble interleukin-2 receptor, and IgG concentrations in cystic fibrosis treated with prednisolone. *Archives of Disease in Childhood* 1994;**71**(1):35-9.

Greally P, Sampson AJ, Piper PJ, Price JF. Effect of prednisolone on airways obstruction in patients with cystic fibrosis [abstract]. *European Respiratory Journal* 1992;**5**(Suppl 15):259s.

Greally P, Sampson AP, Piper AJ, Price JF. Prednisolone reduces airways obstruction in children with cystic fibrosis [abstract]. In: Proceedings of the 11th International Cystic Fibrosis Conference; 1992; Dublin, Ireland. 1992:TS12.

References to studies excluded from this review

Cohen-Cymberknoh 2008 *{published data only}*

Cohen-Cymberknoh M, Blau H, Shoseyov D, Efrati O, Armoni S, Kerem E. Intravenous methylprednisolone pulse therapy vs. oral prednisone for allergic bronchopulmonary aspergillosis (ABPA) in CF [abstract]. *Journal of Cystic Fibrosis* 2008;**7**(Suppl 2):S58. [CFGD REGISTER: PI219a] 5500100000003257

Cohen-Cymberknoh M, Blau H, Shoseyov D, Mei-Zahav M, Efrati O, Armoni S, et al. Intravenous monthly high-dose pulse methylprednisolone vs oral prednisone for therapy of allergic bronchopulmonary aspergillosis in cystic fibrosis [abstract]. *American Journal of Respiratory and Critical Care Medicine* 2009;**179 Suppl**:Abstract no: A1184. [CFGD REGISTER: PI219b] 5500100000010588

Dovey 2007 *{published data only}*

Dovey M, Aitken ML, Emerson J, McNamara S, Dorman D, Gibson RL. A randomised, double-blind, placebo-controlled trial of oral corticosteroid therapy in cystic fibrosis patients hospitalized for pulmonary exacerbations [abstract]. *Pediatric Pulmonology* 2004;**38 (Suppl 27)**:301.

Dovey M, Aitken ML, Emerson J, McNamara S, Waltz DA, Gibson RL. Oral corticosteroid therapy in cystic fibrosis patients hospitalized for pulmonary exacerbation: a pilot study. *Chest* 2007;**132**(4):1212-8.

Linnane 2001 *{published data only}*

Linnane SJ, Thin AG, Keatings VM, Moynihan JB, McLoughlin P, FitzGerald MX. Glucocorticoid treatment reduces exhaled nitric oxide in cystic fibrosis patients. *European Respiratory Journal* 2001;**17**(6):1267-70.

Pantin 1986 *{published and unpublished data}*

Pantin CFA, Stead RJ, Hodson ME, Batten JC. Prednisolone in the treatment of airflow obstruction in adults with cystic fibrosis. *Thorax* 1986;**41**(1):34-8.

Stead RJ, Pantin CFA, Hodson ME, Batten JC. Prednisolone in the treatment of airflow obstruction [abstract]. In: Proceedings of the 13th Annual Meeting of the European Working Group for Cystic Fibrosis; 1985 November 3-8; Jerusalem, Israel. 1985:112.

References to studies awaiting assessment

Kapustina 2008 *{published data only}*

Kapustina T, Fedorova V, Voronkova A, Kapranov N. Long-term treatment with corticosteroids and bone mineral density in patients with cystic fibrosis [abstract]. In: European Respiratory Society Annual Congress; 2008 Oct 4-8; Berlin, Germany. 2008:214s.

Nyamugunduru 1998 *{unpublished data only}*

Nyamugunduru G, Desai M, Rayner RJ, Simmonds E, Weller P, Spencer DA. A double blind parallel placebo-controlled randomised study of oral prednisolone in acute respiratory exacerbations in children with cystic fibrosis. *Thorax* 1998;**53**(Suppl 4):A61.

* Nyamugunduru G, Desai M, Spencer D, Clarke J, Weller P. A double blind parallel placebo-controlled randomised study of the addition of short-course oral prednisolone in treatment of acute respiratory exacerbations in children with cystic fibrosis [abstract]. In: Proceedings of 22nd European Cystic Fibrosis Conference, 1998 June 13-18; Berlin. 1998:79.

Nyamugunduru G, Desai M, Weller P, Spencer DA. The effect of oral prednisolone on serum interleukin-8 concentrations in acute respiratory exacerbations in children with cystic fibrosis [abstract]. In: Proceedings of 13th International Cystic Fibrosis Congress; 2000 June 4-8; Stockholm. Stockholm, 2000:183.

Pukhalsky 2007 *{published data only}*

Pukhalsky A, Shmarina G, Pukhalskaya D, Perederko L, Kashirskaya N, Kapranov N. Can different approaches to anti-inflammatory therapy result in different outcomes in cystic fibrosis patients? [abstract]. In: Proceedings of European Respiratory Society Annual Congress; 2007 Sep 15-19; Stockholm, Sweden. 2007:31s, Abstract no: E345. [CFGD REGISTER: IB96] 5500100000010731

Pukhalsky 2008 *{published data only}*

Pukhalsky A, Shmarina G, Pukhalskaya D, Perederko L. Whether low frequency of hepatobiliary abnormalities in cystic fibrosis patients is associated with anti-inflammatory treatment? [abstract]. In: European Respiratory Society Annual Congress; 2008 Oct 4-8; Berlin, Germany. 2008:216s.

Additional references

Armstrong 1995

Armstrong DS, Grimwood K, Carzino R, Carlin JB, Olinsky A, Phelan PD. Lower respiratory tract infection and inflammation in infants with newly diagnosed cystic fibrosis. *BMJ* 1995;**310**(6994):1570-2.

Balfour-Lynn 1996

Balfour-Lynn IM, Dinwiddie R. Role of corticosteroids in cystic fibrosis lung disease. *Journal of the Royal Society of Medicine* 1996;**89**(Suppl 27):8-13.

Donati 1990

Donati MA, Haver K, Gerson W, Klein M, McLaughlin FJ, Wohl MEB. Long-term alternate day prednisone therapy in cystic fibrosis [abstract]. *Pediatric Pulmonology* 1990;**Suppl 5**:322.

Frisancho 1990

Frisancho AR. Anthropometric standards for the assessment of growth and nutritional status. Ann Arbor: University of Michigan Press, 1990.

Higgins 2003

Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ* 2003;**327**(7414):557-60.

Higgins 2009

Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.0.2 [updated September 2009]. The Cochrane Collaboration, 2008. Available from www.cochrane-handbook.org.

Khan 1995

Khan TZ, Wagener JS, Bost T, Martinez J, Accurso FJ, Riches DWH. Early pulmonary inflammation in infants with cystic fibrosis. *American Journal of Respiratory and Critical Care Medicine* 1995;**151**(4):1075-82.

Konstan 1993

Konstan MW, Berger M. Cystic Fibrosis. New York: Marcel Dekker Inc, 1993.

Konstan 1994

Konstan MW, Hilliard KA, Norvell TM, Berger M. Bronchoalveolar lavage findings in cystic fibrosis patients with stable, clinically mild disease suggesting ongoing infection and inflammation. *American Journal of Respiratory and Critical Care Medicine* 1994;**150**(2):448-54.

Konstan 1996

Konstan MW, Berger M. Current understanding of the inflammatory process in cystic fibrosis: onset and etiology [abstract]. In: Proceedings of the 12th International Cystic Fibrosis Conference; 1996 June 16-21; Jerusalem. Jerusalem, 1996.

Lai 1999

Lai HC, Kosorok MR, Allen DB, FitzSimmons SC, Rosenstein BJ, Campbell PW, et al. Long-term growth evaluation in children with cystic fibrosis with history of regular use of alternate-day prednisone therapy [abstract]. *Pediatric Pulmonology* 1999;**Suppl 19**:297.

Lai 2000

Lai HC, FitzSimmons SC, Allen DB, Kosorok MR, Rosenstein BJ, Campbell PW, et al. Risk of persistent growth impairment after alternate-day prednisone treatment in children with cystic fibrosis. *New England Journal of Medicine* 2000;**342**(12):851-9.

Llewellyn-Jones 1994

Llewellyn-Jones CG, Hill SL, Stockley RA. Effect of fluticasone proprionate on neutrophil chemotaxis, superoxide generation, and extracellular proteolytic activity in vitro. *Thorax* 1994;**49**(3):207-12.

Murray 1991

Murray GD. Statistical aspects of research methodology. *British Journal of Surgery* 1991;**78**(7):777-81.

Schleimer 1990

Schleimer RP. Effects of glucocorticoids on inflammatory cells relevant to their therapeutic applications in asthma. *American Review of Respiratory Disease* 1990;**141**:S59-S69.

References to other published versions of this review

Cheng 1999

Cheng K, Ashby D, Smyth RL. Oral steroids for cystic fibrosis. *Cochrane Database of Systematic Reviews* 1999, Issue 4. Art. No: CD000407. [DOI: 10.1002/14651858.CD000407]

Cheng 2011

Cheng K, Ashby D, Smyth RL. Oral steroids for long-term use in cystic fibrosis. *Cochrane Database of Systematic Reviews* 2011, Issue 10. Art. No: CD000407. [DOI: 10.1002/14651858.CD000407.pub2]

Cheng 2013

Cheng K, Ashby D, Smyth RL. Oral steroids for long-term use in cystic fibrosis. *Cochrane Database of Systematic Reviews* 2013, Issue 6. Art. No: CD000407. [DOI: 10.1002/14651858.CD000407.pub3]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Auerbach 1985

Study characteristics	
Methods	Randomised. Double-blinded.
Participants	45 participants recruited aged 1 - 12 years. CF diagnosed on clinical features and raised sweat electrolytes. Mild to moderate pulmonary disease. 24 assigned to placebo group and 21 to prednisone group. 11 participants did not complete study (7 placebo, 4 prednisone) - 2 moved cities, 5 excluded for non-compliance and steroids prescribed to 4 for clinical indications.
Interventions	Prednisone 2 mg/kg (maximum 60 mg) on alternate days or placebo.
Outcomes	The following were measured at baseline and 6 monthly: FEV_1; FVC; PEFR. Liver function tests (aspartate aminotransferase, alkaline phosphatase, bilirubin and lactate dehydrogenase), glycosylated haemoglobin, circulating immune complexes, IgG, IgM, IgA, albumin, total protein, C3, C4, total white cell count, erythrocyte sedimentation rate and haematocrit. Height and weight measurements (not stated how frequently measured) expressed as percentage of mean height or weight for age from reference standards.
Notes	

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but method not stated.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind, but this might not have been possible since at the doses used, it would have been obvious which participants were in the treatment group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	11 participants did not complete study (7 placebo, 4 prednisone) - 2 moved cities, 5 excluded for non-compliance and steroids prescribed to 4 for clinical indications.

Eigen 1995

Study characteristics	
Methods	Randomised within each centre by computer-generated random number sequence in blocks of 6. Double-blinded. Parallel study.

Eigen 1995 *(Continued)*

	Multicentre (15 centres).
Participants	285 participants recruited. CF diagnosed on clinical features and 2 raised sweat chloride (or sweat sodium) values. Inclusion criteria: aged 6 - 14 years; clinical stability without hospitalisation for CF-related problems within 2 months of entry; serum IgG within 2 standard deviations of normal for centre or hypogammaglobulinaemia; reliable performance of lung function tests for at least 6 months prior to enrolling in trial; FEV_1 > 60% predicted and FEV_1/FVC ratio > 60% predicted. Exclusion criteria included previous treatment with oral, inhaled or nasal corticosteroids for more than 2 weeks within 6 months of entry or any form of corticosteroids in previous month, evidence of liver disease, treatment with non-steroidal anti-inflammatory treatment.
Interventions	Prednisone 2 mg/kg or prednisone 1 mg/kg or placebo on alternate days (maximum dose 60 mg). Participants who missed 30% or more of total prescribed study medication were labelled as non-compliant but still included in analysis.
Outcomes	Primary outcomes were lung function (FEV_1, FVC), serum IgG concentrations, growth and hospitalisation rates. Lung function was assessed at baseline and at 6, 12, 18, 24, 30, 36, 42 and 48 months. Serum IgG was measured at baseline and at 3, 6, 12, 24, 36, 42 and 48 months. Height and weight were measured by techniques standardised across all participating centres. Height scores were calculated on the basis of age-stratified normal populations. Adverse events were monitored every 3 months with emphasis on raised blood glucose concentration, cataracts, raised liver enzymes and respiratory infection with unusual organisms (opportunistic infection). Growth was assessed in a 10-year follow-up study.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomised within each centre by computer-generated random number sequence in blocks of 6.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind and same number of tablets given for each regimen, but true blinding might not have been possible since at the doses used, it would have been obvious from treatment effects which participants were in the treatment group.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Participants who missed 30% or more of total prescribed study medication were labelled as non-compliant but still included in analysis.

Greally 1994

Study characteristics

Methods	Randomised. Double-blinded.
Participants	24 participants aged 5.5 years to 19.5 years recruited.

Greally 1994 *(Continued)*

	CF diagnosed by raised sweat sodium (>70 mmol/l) and established respiratory disease (FEV_1 < 85% predicted).
Interventions	Soluble prednisolone 2 mg/kg/ daily for 14 days and then 1 mg/kg/ day on alternate days for 10 weeks (maximum dose 40 mg) or identical inert placebo tablets.
Outcomes	The following were measured at baseline, 14 days and 12 weeks: FEV_1, FVC, Serum interleukin- 1- alpha, interleukin- 2R, IgG. Specific side effects (raised blood pressure, high blood sodium, low blood potassium, fluid retention and glucose intolerance) were looked for at each visit.
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomised, but method not stated.
Allocation concealment (selection bias)	Unclear risk	Unclear.
Blinding (performance bias and detection bias) All outcomes	Unclear risk	Described as double-blind and placebo and prednisolone tablets were identical, but true blinding might not have been possible since at the doses used, it would have been obvious which participants were in the treatment group.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No withdrawals.

CF: cystic fibrosis
FEV1: forced expiratory volume at one second
FVC: forced vital capacity
IgA: immunoglobulin A
IgG: immunoglobulin G
IgM: immunoglobulin M
mmol/l: millimoles per litre
PEFR: peak expiratory flow rate
P. aeruginosa: *Pseudomonas aeruginosa*

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Cohen-Cymberknoh 2008	Trial of treatment of ABPA (a specific condition) rather than part of the general anti-inflammatory management of CF.
Dovey 2007	Steroids given for less than 30 days.
Linnane 2001	Crossover study, each arm lasting 5 days only (9 day washout).
Pantin 1986	Not randomised.

ABPA: allergic bronchopulmonary aspergillosis
CF: cystic fibrosis

Characteristics of studies awaiting classification *[ordered by study ID]*

Kapustina 2008

Methods	Comparison of inhaled and oral steroids; not clear if randomised.
Participants	40 children with cystic fibrosis (23 female, 17 male), aged 5 - 17.4 years. All patients had "severe" phenotype.
Interventions	14 children inhaled corticosteroids for mean (SD) 34.29 (37.62) months (range 6 -120 months). 26 children received oral steroids (0,5 mg/kg every other day) for mean (SD) 33.04 (37.98) months (range 1 - 185 months). All patients received adequate basic therapy including calcium (500-1000 mg/day) and vitamin D (100-400 IU/day) supplementation.
Outcomes	BMD (g/cm^2) in the lumbar spine (L2 - L4)
Notes	Published as abstract only.

Nyamugunduru 1998

Methods	Described as randomised (method not stated), double-blind (not specified who) parallel trial.
Participants	51 children with cystic fibrosis. 3 children excluded - 1 had allergic bronchopulmonary aspergillosis, 2 on nasogastric feeds.
Interventions	14 days of high-dose prednisolone (2 mg/kg once daily, maximum 30 mg daily) compared to placebo in addition to intravenous antibiotics in acute respiratory exacerbations.
Outcomes	Spirometry (FEV_1, FVC), serum IL-8 levels.
Notes	Published as three separate abstracts only, numbers of participants don't agree across the publications (50, 48, 48)

Pukhalsky 2007

Methods	Comparison of azithromycin, prednisolone and no treatment; not clear if randomised.
Participants	136 CF patients (mean (SD) age 12.0 (0.6) years) and 100 healthy children (mean (SD) age 11.5 (0.9) years). Of the 136 CF patients, 83 received no anti-inflammatory treatment, 16 received an alternated course of prednisolone and 37 were treated with azithromycin.
Interventions	No treatment versus alternated prednisolone (0.3 to 0.5 mg/kg body weight every other day) versus azithromycin (500 mg orally 2 times a week).
Outcomes	Levels of plasma cytokines (IL-10, IFNγ, TGF-β1, TNF-α)
Notes	Possibly same trial as Pukhalsky 2008 - trying to contact authors to clarify.

Pukhalsky 2008

Methods	Comparison of azithromycin, prednisolone and no treatment; not clear if randomised.
Participants	160 children with CF and 100 healthy controls. Of the 160 children with CF, 90 received no anti-inflammatory treatment and 70 received anti-inflammatory treatment (either azithromycin or prednisolone).
Interventions	Azithromycin Group (n = 48): 500 mg orally 3 times a week. Prednisolone Group (n = 22): 0.3 mg/kg body weight every other day.
Outcomes	Plasma cytokines including IL-l0, lFNy and TGF-ß1, hepatobiliary abnormalities.
Notes	Possibly same trial as Pukhalsky 2007 - trying to contact authors to clarify.

CF: cystic fibrosis
FEV_1: forced expiratory volume at one second
FVC: forced vital capacity
SD: standard deviation

DATA AND ANALYSES

Comparison 1. Oral corticosteroids (any dose) versus placebo

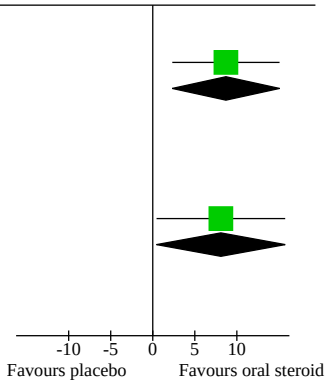
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 Absolute change in per cent predicted FEV1	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.1.1 Up to 2 weeks	1	24	Mean Difference (IV, Fixed, 95% CI)	8.70 [2.32, 15.08]
1.1.2 Up to 12 weeks	1	24	Mean Difference (IV, Fixed, 95% CI)	8.10 [0.45, 15.75]
1.2 Absolute change in per cent predicted FVC	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.2.1 Up to 2 weeks	1	24	Mean Difference (IV, Fixed, 95% CI)	12.81 [4.73, 20.89]
1.2.2 Up to 12 weeks	1	24	Mean Difference (IV, Fixed, 95% CI)	6.70 [-2.12, 15.52]
1.3 Growth retardation (at 4 years)	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3.1 1 mg prednisone	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.3.2 2 mg prednisone	1		Odds Ratio (M-H, Fixed, 95% CI)	Totals not selected
1.4 Height at age over 18 years (boys)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4.1 1 mg prednisone	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.4.2 2 mg prednisone	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.5 Height at over 18 years (girls)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5.1 1 mg prednisone	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.5.2 2 mg prednisone	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6 Absolute change in weight (kg)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.6.1 Up to 12 weeks	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7 Weight at over 18 years (boys)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.1 1 mg prednisone	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.7.2 2 mg prednisone	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8 Weight at over 18 years (girls)	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.1 1 mg prednisone	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.8.2 2 mg prednisone	1		Mean Difference (IV, Fixed, 95% CI)	Totals not selected
1.9 Adverse events	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
1.9.1 Cataracts (1 mg prednisone) (up to 4 years)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
1.9.2 Cateracts (2 mg prednisone) (up to 3 years)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
1.9.3 Diabetes mellitus (1 mg prednisone) (up to 4 years)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
1.9.4 Diabetes mellitus (2 mg prednisone) (up to 3 years)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
1.9.5 Glucosoria (1 mg prednisone) (up to 4 years)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
1.9.6 Glucosoria (2 mg prednisone) (up to 3 years)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
1.9.7 Hyperglycemia (1 mg prednisone) (up to 4 years)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
1.9.8 Hyperglycemia (2 mg prednisone) (up to 3 years)	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected
1.10 Mortality	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.10.1 At 4 years	1		Peto Odds Ratio (Peto, Fixed, 95% CI)	Totals not selected

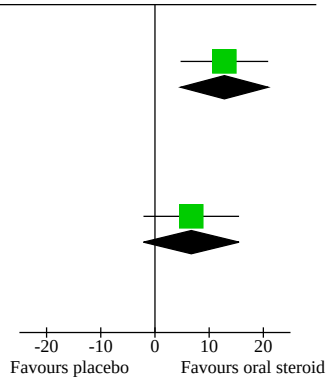
Analysis 1.1. Comparison 1: Oral corticosteroids (any dose) versus placebo, Outcome 1: Absolute change in per cent predicted FEV1

Study or Subgroup	Oral corticosteroid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.1.1 Up to 2 weeks								
Greally 1994	7.7	7.97	12	-1	7.97	12	100.0%	8.70 [2.32 , 15.08]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**8.70 [2.32 , 15.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.67 (P = 0.007)								
1.1.2 Up to 12 weeks								
Greally 1994	6.3	9.56	12	-1.8	9.56	12	100.0%	8.10 [0.45 , 15.75]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**8.10 [0.45 , 15.75]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.08 (P = 0.04)								
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%								



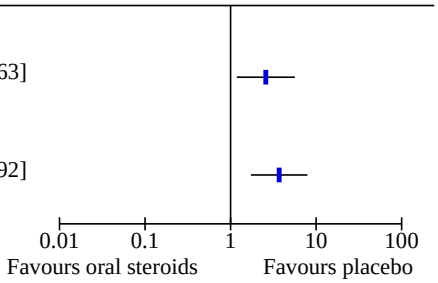
Analysis 1.2. Comparison 1: Oral corticosteroids (any dose) versus placebo, Outcome 2: Absolute change in per cent predicted FVC

Study or Subgroup	Oral corticosteroid Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.2.1 Up to 2 weeks								
Greally 1994	10.4	10.1	12	-2.41	10.1	12	100.0%	12.81 [4.73 , 20.89]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**12.81 [4.73 , 20.89]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 3.11 (P = 0.002)								
1.2.2 Up to 12 weeks								
Greally 1994	4.7	11.02	12	-2	11.02	12	100.0%	6.70 [-2.12 , 15.52]
Subtotal (95% CI)			**12**			**12**	**100.0%**	**6.70 [-2.12 , 15.52]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.49 (P = 0.14)								
Test for subgroup differences: Chi² = 1.00, df = 1 (P = 0.32), I² = 0.2%								



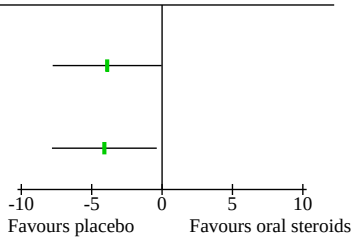
Analysis 1.3. Comparison 1: Oral corticosteroids (any dose) versus placebo, Outcome 3: Growth retardation (at 4 years)

Study or Subgroup	Oral steroids Events	Oral steroids Total	Placebo Events	Placebo Total	Odds Ratio M-H, Fixed, 95% CI
1.3.1 1 mg prednisone					
Eigen 1995	24	95	11	95	2.58 [1.18 , 5.63]
1.3.2 2 mg prednisone					
Eigen 1995	31	95	11	95	3.70 [1.73 , 7.92]



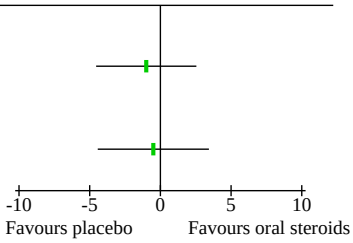
Analysis 1.4. Comparison 1: Oral corticosteroids (any dose) versus placebo, Outcome 4: Height at age over 18 years (boys)

Study or Subgroup	Oral steroids Mean	Oral steroids SD	Oral steroids Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
1.4.1 1 mg prednisone							
Eigen 1995	170.7	7.6	34	174.6	6.8	21	-3.90 [-7.77 , -0.03]
1.4.2 2 mg prednisone							
Eigen 1995	170.5	6.6	31	174.6	6.8	21	-4.10 [-7.82 , -0.38]



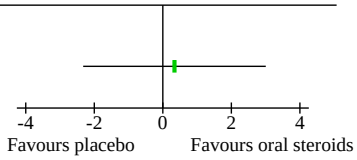
Analysis 1.5. Comparison 1: Oral corticosteroids (any dose) versus placebo, Outcome 5: Height at over 18 years (girls)

Study or Subgroup	Oral steroids Mean	Oral steroids SD	Oral steroids Total	Placebo Mean	Placebo SD	Placebo Total	Mean Difference IV, Fixed, 95% CI
1.5.1 1 mg prednisone							
Eigen 1995	159.3	4.9	20	160.3	6.9	23	-1.00 [-4.54 , 2.54]
1.5.2 2 mg prednisone							
Eigen 1995	159.8	6.7	23	160.3	6.9	23	-0.50 [-4.43 , 3.43]



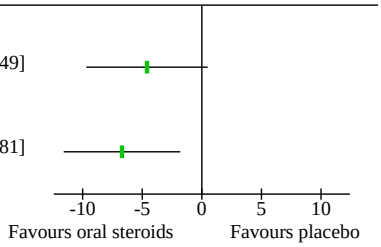
Analysis 1.6. Comparison 1: Oral corticosteroids (any dose) versus placebo, Outcome 6: Absolute change in weight (kg)

Study or Subgroup	Oral corticosteroids Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.6.1 Up to 12 weeks							
Greally 1994	0.35	4.27	13	0.01	2.31	12	0.34 [-2.32 , 3.00]



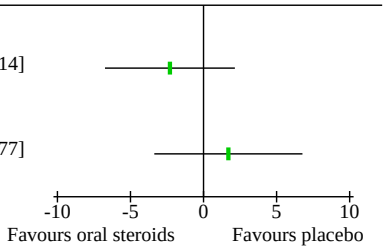
Analysis 1.7. Comparison 1: Oral corticosteroids (any dose) versus placebo, Outcome 7: Weight at over 18 years (boys)

Study or Subgroup	Oral steroids Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.7.1 1 mg prednisone							
Eigen 1995	59.1	9.3	34	63.7	9.4	21	-4.60 [-9.69 , 0.49]
1.7.2 2 mg prednisone							
Eigen 1995	57	7.9	31	63.7	9.4	21	-6.70 [-11.59 , -1.81]



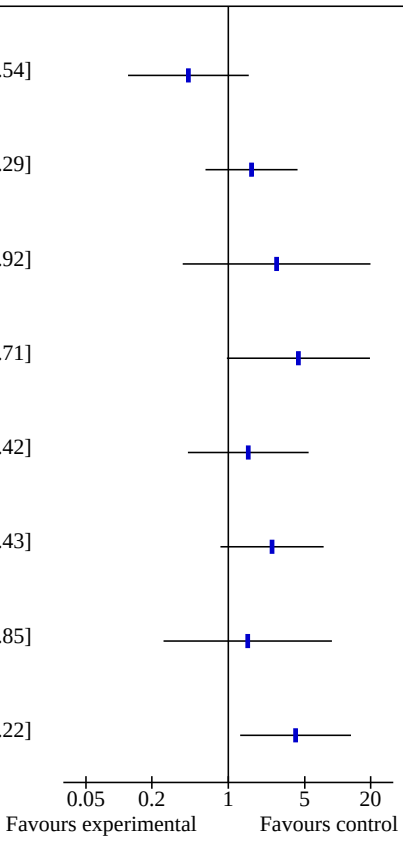
Analysis 1.8. Comparison 1: Oral corticosteroids (any dose) versus placebo, Outcome 8: Weight at over 18 years (girls)

Study or Subgroup	Oral steroids Mean	SD	Total	Placebo Mean	SD	Total	Mean Difference IV, Fixed, 95% CI
1.8.1 1 mg prednisone							
Eigen 1995	49.6	7.6	20	51.9	7.2	23	-2.30 [-6.74 , 2.14]
1.8.2 2 mg prednisone							
Eigen 1995	53.6	10.1	23	51.9	7.2	23	1.70 [-3.37 , 6.77]



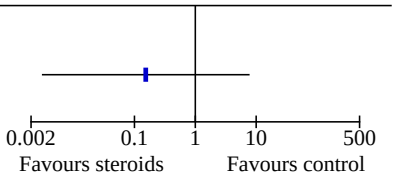
Analysis 1.9. Comparison 1: Oral corticosteroids (any dose) versus placebo, Outcome 9: Adverse events

Study or Subgroup	Oral corticosteroids Events	Total	Placebo Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
1.9.1 Cataracts (1 mg prednisone) (up to 4 years)					
Eigen 1995	3	95	7	95	0.43 [0.12 , 1.54]
1.9.2 Cateracts (2 mg prednisone) (up to 3 years)					
Eigen 1995	11	95	7	95	1.63 [0.62 , 4.29]
1.9.3 Diabetes mellitus (1 mg prednisone) (up to 4 years)					
Eigen 1995	3	95	1	95	2.76 [0.38 , 19.92]
1.9.4 Diabetes mellitus (2 mg prednisone) (up to 3 years)					
Eigen 1995	6	95	1	95	4.37 [0.97 , 19.71]
1.9.5 Glucosoria (1 mg prednisone) (up to 4 years)					
Eigen 1995	6	95	4	95	1.52 [0.43 , 5.42]
1.9.6 Glucosoria (2 mg prednisone) (up to 3 years)					
Eigen 1995	10	95	4	95	2.51 [0.85 , 7.43]
1.9.7 Hyperglycemia (1 mg prednisone) (up to 4 years)					
Eigen 1995	3	95	2	95	1.50 [0.26 , 8.85]
1.9.8 Hyperglycemia (2 mg prednisone) (up to 3 years)					
Eigen 1995	10	95	2	95	4.12 [1.28 , 13.22]



Analysis 1.10. Comparison 1: Oral corticosteroids (any dose) versus placebo, Outcome 10: Mortality

Study or Subgroup	Oral corticosteroids Events	Total	Placebo Events	Total	Peto Odds Ratio Peto, Fixed, 95% CI
1.10.1 At 4 years					
Auerbach 1985	0	21	1	24	0.15 [0.00 , 7.80]



ADDITIONAL TABLES

Table 1. Long-term growth - follow up data at 4 years (Auerbach 1985)

Time	Group I n = 9		Group II n = 5		Group III n = 10		Group IV n = 6	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Baseline	-0.44	0.73	-0.30	0.85	-0.75	0.78	-1.64	0.45
End of study (4 years)	-0.89	0.42	-0.62	0.84	-0.79	0.86	-1.58	0.58
Follow up (10 yrs)	-1.86	0.89	-1.34	1.42	-0.70	0.69	-2.02	0.74

Group I: originally randomised to steroids for 4 years, continued on steroids for mean (SD) 9.5 (1.2) years
Group II: originally randomised to steroids for 4 years, ceased taking steroids after mean (SD) 4.5 (0.46) years
Group III: originally randomised to placebo for 4 years, 5 in this group never received steroids and 5 received variable doses of steroids for mean (SD) 0.6 (0.3) years
Group IV: originally randomised to placebo for 4 years, subsequently received steroids for mean (SD) 3.6 (1.2) years
SD: standard deviation

WHAT'S NEW

Date	Event	Description
8 April 2021	Review declared as stable	Due to a lack of research in this area the Editorial Board of the Cystic Fibrosis and Genetic Disorders Review Group have decided to no longer update this review.

HISTORY

Protocol first published: Issue 1, 1997
Review first published: Issue 1, 1998

Date	Event	Description
1 December 2015	New search has been performed	There are no trials included in the review and we have not identified any relevant trials up to September 2015. We will continue to run searches to identify any potentially relevant trials; however, we do not plan to update other sections of the review until new trials are published.
1 December 2015	New citation required but conclusions have not changed	Since no new trials were included in this update of the review, our conclusions remain the same.
12 August 2013	Review declared as stable	The authors are of the opinion that even though the benefits and risks of this intervention have not yet been as fully delineated, there are unlikely to be any new trials of this intervention undertaken. Therefore, this review will no longer be updated. A search of the Cystic Fibrosis & Genetic Disorders Review Group's Trials Registers will still be undertaken every two years, but the review will not be updated and re-published unless any new data become available.
3 June 2013	New citation required but conclusions have not changed	We have not included any new data in this update of the review and hence our conclusions remain the same.
3 June 2013	New search has been performed	A search of the Cochrane Cystic Fibrosis & Genetic Disorders Cystic Fibrosis Trials Register identified three new references to two studies (all published as abstracts only). Two references relating to a single study have been excluded (Cohen-Cymberknoh 2008) and a further reference has been listed as 'Awaiting assessment' until we are able to contact the authors clarify whether it meets the review's inclusion criteria (Pukhalsky 2007).
24 January 2013	Amended	Contact details updated.
13 June 2011	New citation required and conclusions have changed	The remit of the review has been changed to focus on long-term use of oral steroids, i.e. over 30 days. The use of oral steroids for 30 days or less will be the subject of another Cochrane review. As a result of this change, a study previously included in the review has now been excluded due to duration of treatment (Dovey 2007).
13 June 2011	New search has been performed	A search of the Cystic Fibrosis Trials Register identified two new studies which were potentially eligible for inclusion in this review (Kapustina 2008; Pukhalsky 2008). Due to a lack of information

Date	Event	Description
		relating to our inclusion criteria, both these studies have been listed as 'Awaiting classification' until we are able to clarify details with the primary investigators.
9 November 2009	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register did not identify any new references potentially eligible for inclusion in this review.
1 October 2009	Amended	Clarified weight data from Greally study with authors and included in the review.
8 January 2009	New search has been performed	One study has been moved from 'Awaiting classification' and is now included in the review (Dovey 2007a).
28 August 2008	New search has been performed	A search of the Group's Cystic Fibrosis Trials Register identified one reference, which was an additional reference to a study already listed as 'Awaiting classification' (Dovey 2007a). We plan to assess this study for the next update.
27 August 2008	Amended	Converted to new review format.
23 May 2007	New search has been performed	A search was run in November 2006, and references to two new studies were identified. One study was not eligible for inclusion as the treatment was not for an exacerbation and is listed in 'Excluded studies' (Linnane 2001). The other study has been listed as 'Awaiting assessment' until further details can be obtained from the authors (Dovey 2004).
23 February 2006	New search has been performed	A search was run in November 2005, and one new reference was identified which was an additional reference to an already included study (Greally 1992). There was no new information available from this reference.
23 February 2005	New search has been performed	A search was run in August 2004, but no new references were identified for inclusion in, or exclusion from this review.
19 November 2003	New search has been performed	A search was run in October 2003, but no new references have been found.
19 November 2003	Amended	Some minor changes have been made to the text following comments from the medical statistician at the editorial base.
22 April 2002	New search has been performed	Date of the most recent search of the Group's trials register: April 2002, no new references were found.
1 July 1999	New citation required and conclusions have changed	Substantive amendment, re-formatted.

CONTRIBUTIONS OF AUTHORS

Rosalind Smyth and Katharine Cheng conceived the review and wrote the protocol. They both independently assessed studies for inclusion in the review. Katharine Cheng wrote the review with assistance from Rosalind Smyth and Deborah Ashby and has performed the updates of the review. She also acts as guarantor of the review.

DECLARATIONS OF INTEREST

The lead author (KC) of this review has been employed by GlaxoSmithKline Research and Development Ltd since autumn 2004. GlaxoSmithKline does not produce or market any drugs that may fall into the scope of this review.

The remaining authors (RS and DA) declare no potential conflict of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- NHS North West Region R & D Programme, UK

INDEX TERMS

Medical Subject Headings (MeSH)

Administration, Oral; Anti-Inflammatory Agents [*administration & dosage] [adverse effects]; Cystic Fibrosis [*complications]; Early Termination of Clinical Trials; Glucocorticoids [*administration & dosage] [adverse effects]; Growth [drug effects]; Prednisolone [administration & dosage] [adverse effects]; Randomized Controlled Trials as Topic; Respiratory Tract Diseases [*drug therapy] [etiology]; Sex Factors

MeSH check words

Child; Female; Humans; Male