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[Intervention Review]

Corticosteroids for idiopathic pulmonary fibrosis

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ABSTRACT

Background

Idiopathic pulmonary fibrosis (IPF) is a disease with significant morbidity and mortality. Patients short survival time, high mortality and generally rapid decline raise the importance of early treatment. Current guidelines suggest a combination of corticosteroids and immunosuppressants as "gold standard" for IPF treatment, although the evidence for this recommendation is weak. Based on animal models, it has been hypothesized a central role for aberrant wound healing following repeated epithelial lung injury, weakening the rationale for using corticosteroids in IPF, previously thought to be a chronic inflammatory disease.

Objectives

The aim of the review is to determine the efficacy of corticosteroids in the treatment of adults with familial and sporadic IPF.

Search methods

We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2008), MEDLINE (January 1966 to June 2008) and EMBASE (January 1985 to June 2008) and reference lists of articles. We searched reference lists of published articles to identify clinical trials.

Selection criteria

Randomised controlled trials (RCT) and controlled clinical trials (CCT) using corticosteroids alone for the treatment of adults with IPF.

Data collection and analysis

Abstracts of identified articles were retrieved and articles possibly fulfilling inclusion criteria were retrieved in full. Two reviewers would have independently assessed trial quality if there had been any included study.

Main results

Seventeen articles were selected as potentially eligible for meta-analysis. After further analysis of full text papers, no RCTs or CCTs were identified as suitable and therefore no data was available for inclusion in any meta-analysis. All studies were excluded due to inadequate methodologies.

Authors' conclusions

At present, there is no evidence for an effect of corticosteroid treatment in patients with IPF. On the other hand, other fibrotic lung diseases, such as non-specific interstitial pneumonia (NSIP), are reported to show a better response to corticosteroids. Making a clear

distinction between IPF and other entities grouped under the umbrella term *interstitial lung disease* is, therefore, essential as this may have therapeutic and prognostic implications.

PLAIN LANGUAGE SUMMARY

Currently there is no evidence to support the routine use of corticosteroids alone in the management of idiopathic pulmonary fibrosis.

Idiopathic pulmonary fibrosis (IPF) is a chronic disorder of unknown cause that is progressive and leads to death. Existing evidence about the treatment of IPF is difficult to interpret because of evolving diagnostic criteria and classification schemes, grouping together diverse entities with markedly different natural histories and responses to therapy. Therefore, because the old studies did not include only IPF patients, their results cannot be extended to IPF as they are currently defined. In addition, methodologic problems mainly related to the lack of randomized placebo-controlled treatment trials have made evidence-based conclusions difficult. A systematic search for high quality placebo-controlled randomised trials comparing corticosteroid treatment with placebo in subjects with a diagnosis of IPF was unable to identify any studies suitable for inclusion in the review.

BACKGROUND

Idiopathic pulmonary fibrosis (IPF) is a specific form of chronic interstitial pneumonia limited to the lung, associated with the pathologic pattern of usual interstitial pneumonia (UIP) on lung biopsy, with patchy involvement, architectural distortion, microcystic changes with honeycombing or marked smooth muscle metaplasia/hyperplasia, and frequent subpleural or paraseptal distribution (ATS 2002). Most patients are middle aged and a predominance of males has been reported (ATS 2002). In the presence of a compatible biopsy, the diagnosis of IPF is based on: (1) the exclusion of other causes of interstitial lung disease (ILD); (2) an abnormal pulmonary function test showing a restrictive pattern and/or decreased diffusing lung capacity (DLCO); and (3) a radiologic pattern showing bibasal reticular abnormalities with ground glass appearance (ATS 2002). The clinical course of IPF is progressive in the vast majority of cases and can be relentless or insidious; the mean survival in recent studies ranges from two to four years after diagnosis (Kim 2006).

The main diagnostic problem is to distinguish IPF from other idiopathic interstitial pneumonia with similar clinical presentation. Usually, these entities, show a different response to steroids and a better outcome. Non-specific interstitial pneumonia (NSIP), the most common idiopathic interstitial pneumonia after IPF, may display a clinical presentation similar to IPF, but its histology is characterised by a more homogeneous appearance of both inflammation or fibrosis as opposed to the temporal and spatial heterogeneity seen in IPF. The radiologic pattern in NSIP is most frequently characterized by alveolar opacities (*ground glass*); linear infiltrates or honeycombing are rarely seen at presentation. Response to steroid treatment has been observed (du Bois 2007).

Some other forms of idiopathic interstitial pneumonias, including desquamative interstitial pneumonia (DIP), respiratory bronchiolitis-associated interstitial lung disease (RB-ILD), idiopathic bronchiolitis obliterans with organizing pneumonia (idiopathic BOOP), amongst others, may be steroid-responsive.

Since its first description, IPF has been recognized as a distinct entity with lesions that vary in age and location raising important questions about the classical view that IPF was a disease in which parenchymal fibrosis was directly caused by chronic inflammation. This prior hypothesis suggested that an unidentified insult initiated a cycle of chronic inflammatory injury leading to fibrosis. As a consequence, corticosteroids have been the mainstay of IPF treatment. In contrast, based on current diagnostic criteria for IPF, there have been no or poor response rates to corticosteroids for such patients (Gross 2001). According to a current evolving hypothesis, an abnormal wound healing process in response to multiple sites of ongoing epithelial injury and activation is associated with the formation of patchy fibroblast-myofibroblast foci, which evolve to fibrosis (Selman 2001). In this scenario, there would be little or no rationale for the use corticosteroids in IPF.

OBJECTIVES

The objective of this review was to determine the efficacy of corticosteroids in IPF treatment.

METHODS

Criteria for considering studies for this review

Types of studies

We considered randomised controlled trials (RCT) and controlled clinical trials (CCT) for inclusion.

Types of participants

Adult patients with histological evidence of IPF or with a diagnosis based on clinical and radiologic criteria consistent with ATS/ERS 2002 consensus (ATS 2002).

Types of interventions

Oral or inhaled corticosteroids, administered for more than two months, versus placebo, although both interventions were to be analysed separately. Interventions involving other drugs for the treatment of IPF will be excluded.

Types of outcome measures

Primary outcomes

- Mortality

Secondary outcomes

- Symptom scores including dyspnoea at rest, dyspnoea on exertion, cough
- Quality of life using a validated health status questionnaire
- Exercise capacity as assessed by exercise tests
- Arterial blood gases
- Days sick as assessed by hospital admissions
- Lung function measured by forced expiratory volume in 1 second (FEV1), peak expiratory flow rate (PEF), forced vital capacity (FVC), diffusing lung capacity (DLCO and DLCO/Va)
- Changes on chest x-ray and/or chest High Resolution Computed Tomography (HRCT) using standardised radiographic scores.
- Number and type of adverse effects
- Patient preference
- Number of study withdrawals

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (The Cochrane Library Issue 2, 2008), MEDLINE (January 1966 to June 2008) and EMBASE (January 1985 to June 2008).

For the full database search strategies please see [Appendix 1](#), [Appendix 2](#) and [Appendix 3](#).

Searching other resources

We searched reference lists of published articles to identify trials.

Data collection and analysis

Selection of studies

Two reviewers (PS and LF) reviewed abstracts of articles identified using the search strategy above, and retrieved the full articles that appeared to fulfil the inclusion criteria. Data on at least one

of the outcome measures had to be included in the study. We reviewed each article identified and categorized them into one of the following groups:

- included: RCT or CCT meeting the described inclusion criteria and those where it was impossible to tell from the abstract, title or MESH headings;
- excluded: non RCT or CCT.

In cases if in doubt, a third reviewer assessed the article and consensus was reached.

Assessment of risk of bias in included studies

The methodological quality of each trial was to be assessed using a 0 to 5 scale based upon the method described by Jadad ([Jadad 1996](#)) and summarised as follows:

- (1) Is the study described as randomised? (yes = 1; no = 0)
- (2) Is the study described as double blind? (yes = 1; no = 0)
- (3) Is there a description of withdrawals and dropouts? (yes = 1; no = 0)
- (4) Is the method of randomisation well described and appropriate? (yes = 1; no = 0)
- (5) Is the method of double blinding well described and appropriate? (yes = 1; no = 0)
- (6) Deduct 1 point if methods for randomisation or blinding are inappropriate.

In addition each study was assessed for the reliability of the diagnosis of IPF using pre-specified criteria (see above).

Data synthesis

We intended combining outcomes from included trials using the Review Manager software. Sensitivity analysis based on study quality was to be performed if there had been included studies. We would also have carried out tests for heterogeneity and random effects models would have been used if heterogeneity was found.

RESULTS

Description of studies

Included studies

There were no RCTs or CCTs comparing corticosteroid therapy to placebo. We did not undertake any meta-analysis.

Excluded studies

[Gay 1998](#) and co-workers studied 38 patients with open lung biopsy-proven IPF, with the aim of identifying pre-treatment features potentially useful to predict: (1) short term improvement in pulmonary function; and (2) longer term survival. All participants had an histological diagnosis of IPF, but diagnostic criteria were different from the ATS 2000 criteria (ATS 2000). At baseline, a score was generated for each participant combining clinical, radiographic and physiological information (CRP score). All participants were then treated for three months with high-dose steroids (prednisone 1mg/Kg/day) and CRP scoring was repeated. Three groups of participants (responders, stable, non-responders) were identified based on the pre/post CRP score. Therapy was continued for long term follow up (greater than one year), as follows: corticosteroids in responders, in a tapering dose over 18 months; in all others, corticosteroids were rapidly reduced and

discontinued within four weeks and participants were crossed over to oral cyclophosphamide (2mg/Kg/day) for a six-month course of therapy. The study demonstrated that pre-therapy pulmonary function, pathologic and radiographic parameters are different in individuals who respond to initial prednisone therapy. Only high resolution computer tomography (HRCT) imaging and pathologic fibrosis reliably predicted long-term survival in patients with biopsy-proven IPF. This study was not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo and was therefore excluded.

[Hanson 1995](#) and co-workers investigated changes in pulmonary function after one year of treatment to see if they were predictive of survival in patients with IPF, with a retrospective evaluation of a series of patients. The study group consisted of 58 IPF participants who were being treated for their condition, who survived for at least one year from the time of initiation of treatment and had forced vital capacity (FVC) measurements at the time of diagnosis, at 9 and 15 months. Forty four patients also had a single-breath diffusing capacity (Dsb) measured at the time of diagnosis, at 9 and 15 months and 33 participants had an arterial blood gas analysis at the time of diagnosis, at 9 and 15 months. IPF diagnosis was based on radiological and histological criteria but because of the lack of a clear indication of the histopathological findings for these participants, they cannot be surely defined as affected by IPF according to ATS 2000 definition (ATS 2000). Treatment varied among participants: 20 received prednisone alone, 26 prednisone/azathioprine, 5 prednisone/cyclophosphamide, 7 switched from prednisone/azathioprine to prednisone/cyclophosphamide during the follow-up. After one year of treatment, based on the three pulmonary function tests, patients' conditions were classified as improved, unchanged or worse. Survival analysis was carried out to analyse survival time in relation to change in pulmonary function after the year of therapy. The authors concluded that changes in FVC and Dsb after one year of treatment are strongly predictive of duration of survival in IPF patients. This study was not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo and it was therefore excluded.

[Kang 1999](#) and co-workers retrospectively evaluated the short-term efficacy of steroid and immunosuppressive therapy for 20 IPF patients. Patients were identified by thorascopic lung biopsy. Participants underwent baseline evaluation including clinical history, pulmonary function test, bronchoalveolar lavage (BAL) and HRCT. Fourteen participants received high dose steroids for 8 to 12 weeks (prednisolone 1 mg/Kg/day) and then corticosteroids were gradually reduced to low dose prednisolone (0.25 mg/Kg/day). Six participants received oral cyclophosphamide (2 mg/Kg/day) with/without low dose prednisolone. Participants were classified as responders or non-responders on the basis of changes in clinical, functional or HRCT parameters after a six months follow-up. Authors found that histopathological diagnoses of responders were all NSIP and those of non-responders were all UIP. Participants with NSIP or lymphocytosis in BAL were more likely to respond to steroid or immunosuppressive therapy. This study was not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo and it was therefore excluded.

[Turner-Warwick 1980](#) and co-workers retrospectively evaluated 220 IPF participants to study which factors could influence early response to treatment and the influence of steroid treatment on survival. It is not clear if the diagnostic criteria in the ATS 2000 definition (ATS 2000) were adhered to. One hundred and forty three

participants had received steroids and were therefore evaluated. twenty four participants received prednisone/prednisolone at a dose of 10 to 15 mg/day, 30 participants received 20 to 25 mg/day, 35 participants received 30 to 35 mg/day, 29 participants received 40 to 45 mg/day and 14 participants 50 to 60 mg/day. For 11 participants dosage was unknown. The influence of corticosteroid treatment was assessed in terms of clinical, radiographic and physiological response after four to eight weeks of treatment and in terms of survival. Participants were classified as responders and non-responders. The only significant features associated with a good steroid response were younger age and less severe dyspnoea at presentation. Treated participants with an early good response to steroids had better survival than non responders. This study was not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo and it was excluded.

[Gulsvik 1986](#) and co-workers conducted a pilot study to examine in a small group of patients if an initial high pulse dose of methylprednisolone could induce a more extensive improvement in respiratory symptoms and lung function tests, than a low dose of prednisolone after three and six weeks of therapy. Participants were selected on the basis of clinical criteria, thus they cannot be surely defined as affected by IPF according to ATS 2000 definition (ATS 2000). Five participants were randomised to high dose methylprednisolone (1 g intravenously every second day in total five doses during 10 days, then prednisolone was given for six days with decreasing doses from 60 mg until a daily dose of 30 mg was maintained) and five to conventional dose prednisolone (30 mg prednisolone daily divided into two doses). After three weeks of treatment the high dose group had received a total dose of steroids with an anti-inflammatory potency more than 10 times greater than the low-dose group. Neither symptoms nor lung function tests differed significantly between the two groups after three and six weeks of therapy. This study was excluded because it was not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.

[Douglas 1998](#) and co-workers conducted a RCT comparing high dose prednisone (n = 12) to colchicine (n = 14) for the treatment of IPF. Diagnosis was according to ATS 2000 definition (ATS 2000). The minimum dose of prednisone was 60 mg/day for 1 month, tapered gradually to 40 mg every other day by the end of the third month, with subsequent doses determined by the clinical response. In the colchicine arm the dose was 0.6 to 1.2 mg/day at the highest dose tolerated by the participant. Median length of follow-up was 1.5 years. Participants treated with high-dose prednisone showed a higher incidence of serious side effects and exhibited a non statistically significant trend to more rapid decline of pulmonary function and shorter survival than those treated with colchicine. In most participants with a UIP diagnosis, neither drug resulted in objective improvement and the disease continued to progress in most cases. The authors conclude that colchicine appears to be a safer alternative to high dose prednisone, but may be no different than no therapy. This trial was excluded because it involved drugs (colchicine) other than oral or inhaled corticosteroids.

[Johnson 1989](#) and co-workers conducted a RCT comparing prednisolone (n = 22) to cyclophosphamide plus prednisolone (n = 21) for the treatment of IPF. In the prednisolone only series participants received prednisolone 60 mg daily for one month then reduced by 5 mg at week to 20 mg on alternate days or the minimum dose to maintain early improvement. Participants in the cyclophosphamide/prednisolone series received 100, 110 or 120

mg cyclophosphamide daily depending on body weight plus 20 mg prednisolone on alternate days. All participants were followed up for at least three years and 33 participants for five years or more. For response to treatment participants were classified as improved, stable or deteriorating on the basis of change in breathlessness score, radiographic appearance and lung function. The authors conclude that cyclophosphamide in combination with low dose prednisolone is at least as effective as a course of high dose corticosteroids followed by an alternate day low dose regimen. However, both drugs were effective only in a small proportion of participants. There was a suggestion of improved survival in participants allocated to the cyclophosphamide-prednisolone regimen, but this was not significant. This trial was excluded because it involved drugs (cyclophosphamide) other than oral or inhaled corticosteroids.

[Selman 1998](#) and co-workers conducted a non-randomised study to compare the long term effects of colchicines/D-penicillamine in association to prednisone versus prednisone alone in the treatment of IPF. Fifty six patients were included: 19 received colchicine/prednisone, 11 D-penicillamine/prednisone, 11 D-penicillamine/colchicine/prednisone and 15 prednisone alone. Prednisone therapy was started at 1.0 mg/kg/day for one month followed by a biweekly taper to maintenance dose of 15 mg/day Colchicine was administered at a dose of 1.0 mg daily and D-penicillamine at a daily dose of 600 mg. IPF was confirmed by biopsy specimen. The histological criteria for the diagnosis of IPF were not the same as those reported in the ATS 2000 statement (ATS 2000) and neither were the radiological criteria. Response to treatment was assessed by considering survival and changes in dyspnoea score, lung function tests and arterial blood gas analyses at one and two years. No statistically significant differences were found in dyspnoea score, lung function tests and arterial gas analyses at baseline and after one and two years. No difference in survival was found. The authors concluded that neither colchicine nor D-penicillamine modified the progressive course of prednisone-treated IPF. This study was excluded because it was not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.

[O'Donnell 1987](#) and co-workers conducted a non-randomised prospective study to assess the effect of cyclophosphamide in comparison to prednisone on the neutrophil component of the alveolitis in IPF. Twenty eight IPF participants were enrolled. All participants were diagnosed with IPF according to previously defined criteria, including open lung biopsy. Because of the lack of a clear indication of the histopathological findings for these participants, they cannot be surely defined as affected by IPF according to ATS 2000 definition (ATS 2000). Participants were assigned to four treatment groups, according to their alveolitis features and evaluated by BAL at three and six months:

1. eight never treated patients, in whom neutrophils represented $\geq 10\%$ of cells in BAL, were treated with prednisone alone (1 mg/kg for four weeks with subsequent taper at 5 mg every 10 days to a maintenance level of 0.25 mg/kg);
2. six never treated patients, in whom neutrophils represented $< 10\%$ of cells in BAL, were treated with prednisone alone (1 mg/kg daily for four weeks with subsequent taper at 5 mg every 10 days to a maintenance level of 0.25 mg/kg);

3. five never treated patients, in whom neutrophils represented $\geq 10\%$ of cells in BAL, were treated with cyclophosphamide alone (1.5 mg/kg daily for the study period);
4. nine patients, receiving prednisone (for at least three months), with a neutrophil alveolitis $\geq 10\%$, were treated with a continuation of prednisone at the same dose and with the addition of cyclophosphamide (1.5 mg/kg daily for the study period).

No significant differences were found among neutrophils proportion in the prednisone groups at three and six months compared to pre-treatment levels. A significant reduction in neutrophil proportion was found in the cyclophosphamide group. In participants receiving prednisone, the addition of cyclophosphamide determined a significant reduction in neutrophil proportion at three months. The authors concluded that the significant reduction in neutrophil component in BAL following cyclophosphamide treatment was a promising alternative to steroids alone in the treatment of IPF. This study was excluded because it was not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.

[Douglas 1997](#) and co-workers retrospectively assessed the clinical effect of colchicine ($n = 22$) compared to steroids ($n = 22$) in the treatment of UIP. The 22 participants treated with colchicine were selected among 98 patients treated in the Mayo Clinic on the basis of inclusion criteria comprising progressive dyspnoea, bibasilar inspiratory crackles, typical chest X-rays, lung function tests consistent with UIP, HRCT with characteristic findings of UIP or proven UIP at open lung biopsy. For the control group, 22 patients with proven UIP on lung biopsy were extracted from an historical database of 102 patients treated with prednisone. Authors acknowledged that the two groups differed in selection criteria, although adherence to ATS 2000 criteria (ATS 2000) was good. Seven participants in the colchicine group took 0.6 mg daily while 15 took 0.6 mg twice daily. Of the 22 participants on prednisone, eight began with daily treatment and 14 with an alternate-day dosage. At one year, two patients were receiving daily prednisone therapy (mean dosage 40 mg/day), nine were taking prednisone on alternate days (mean dosage 42.2 mg every other day), two had discontinued prednisone and one began a different treatment. Forced vital capacity (FVC), diffusing lung capacity (DLCO), total lung capacity (TLC) and post-exercise oxygen saturation (SO_2) at the start and after two years were compared by fitting a linear regression model with data from all PFTs performed in the follow-up period. The Kaplan Meier method was used to estimate cumulative failure probability in the two groups. No significant difference was found in the rate of change of all the PFT examined and in failure curves. Several participants in the colchicine group experienced diarrhoea but did not require discontinuation of colchicine therapy. One participant experienced thinning of the hair and one experienced testicular failure, but this effect was not ascribed to colchicine. In the steroids group, 10 participants reported no side effect, four reported weight gain, four hyperglycaemia, four emotional lability, three muscle weakness, three osteoporosis and fractures of the spine, two depression, one cushingoid features, one cataract and one gastritis with bleeding. This study was excluded because it was not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.

[Behera 1998](#) and co-workers retrospectively assessed the effect of steroid therapy in patients with IPF. Diagnostic criteria

comprised clinical, radiological, respiratory function criteria and transbronchial biopsy when possible, with low correspondence to ATS 2000 criteria (ATS 2000). Fifty IPF participants received prednisone 1 mg/kg/day for six weeks which was then tapered to a maintenance dose. A subjective improvement in symptoms was reported by 26 participants in the first three to six months of therapy. Subsequently they either deteriorated or remained stable. No clinical improvement was reported for 20 participants and no radiological improvement in any case. A significant improvement was reported for FVC only at three months compared to the baseline, subsequently there was no significant improvement. Three participants showed an improvement of FVC at six months and one at one year. Five patients had a decrease in FVC by 10% or more. One patient developed pulmonary tuberculosis after nine months of therapy. The authors concluded that, despite an initial improvement, steroid therapy was a not satisfactory treatment for IPF. This study was excluded because it was not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.

[Ziesche 1999](#) and co-workers carried out a RCT to study the effect of the adjunct of interferon gamma-1b to low dose prednisolone in patients with IPF. Inclusion criteria comprised a histological diagnosis of IPF and previous treatment failure as documented by worsening of lung function in the 12 months prior to the study. Inclusion criteria did not completely fulfil the ATS 2000 criteria (ATS 2000). Nine participants were randomised to interferon gamma-1b 200 mg subcutaneously three times per week plus 7.5 mg of oral prednisolone daily for 12 months; nine patients were randomised to 7.5 mg of oral prednisolone daily for 12 months. At 12 months, the absolute decrease of TLC was 4% in the prednisolone group, while the interferon/prednisolone group experienced an absolute increase of TLC of 9%. Similar changes were reported for partial pressure of arterial oxygen at rest and for partial pressure of arterial oxygen on maximal exertion. All patients receiving interferon gamma-1b/prednisolone reported an improvement in the activities of daily living, but these were not formally evaluated. All patients receiving interferon experienced fever and chills during the first three weeks of treatment and three had bone and muscle pain. All side effects subsided within the first 9 to 12 weeks of treatment. The main side effects in the prednisolone group were hyperglycemia, weight gain and skin changes. Authors concluded that interferon gamma-1b was a promising treatment for IPF but its efficacy and safety needed to be confirmed by larger studies. This trial was excluded because it involved drugs (interferon gamma-1b) other than oral or inhaled corticosteroids.

[Raghu 1991](#) and co-workers carried out a RCT to assess the efficacy of azathioprine combined to prednisone versus prednisone alone in the treatment of IPF. Inclusion criteria comprised histological features and lung function tests compatible with IPF diagnosis, radiological and clinical progressive worsening and exclusion of other causes. Transbronchial lung biopsy was used to establish a diagnosis only in four patients who refused open lung biopsy. There was a good adherence to ATS 2000 criteria (ATS 2000) even if UIP pattern was not considered as the main feature for diagnosis. Twenty seven IPF patients were randomised to either: (1) azathioprine at a daily dose of 3 mg/kg/day (max dose 200 mg/day) to the nearest 25 mg dose increment for the duration of the trial plus oral prednisone from 1.5 mg/kg/day (max dose 100 mg/day) for the first two weeks till a maintenance dose of 20 mg/day or less according to patients tolerance ($n = 13$); (2) oral prednisone from 1.5 mg/kg/day (max dose 100 mg/day) for the first

two weeks till a maintenance dose of 20 mg/day or less according to patients tolerance plus a similar number of placebo tablets ($n = 14$). Follow up duration was 12 months with clinical assessment every three months. Four participants in each group died before completing one year of treatment and three participants crossed to the azathioprine group because of clinical deterioration. Neither lung function tests or survival differed significantly between the two groups. Adjusting for age as a continuous variable in the Cox model resulted in a marginally significant advantage in the azathioprine group ($p = 0.05$). Authors concluded that the trend for improved survival in patients receiving azathioprine needed to be better investigated in larger studies. This trial was excluded because it involved drugs (azathioprine) other than oral or inhaled corticosteroids.

[Keogh 1983](#) and co-workers carried out a RCT to assess the effect of intermittent high dose parenteral corticosteroids on the neutrophil alveolitis of IPF. All participants had an histological diagnosis of IPF, but diagnostic criteria were different from ATS 2000 criteria (ATS 2000). Thirteen IPF participants were randomised to one of two groups: (1) five patients receiving orally low dose corticosteroids daily (prednisone 0.25 mg/kg daily or its equivalent) plus weekly intravenous pulses of 2 g of methylprednisolone; (2) eight patients receiving orally low dose corticosteroids daily (prednisone 0.25 mg/kg daily or its equivalent). Follow-up time was six months. A statistically significant difference was found in the decrease of neutrophil component of BAL and in the gallium (^{67}Ga) uptake in chest scans. No significant difference was found in blood test and lung function test from baseline values. Some patients experienced metallic taste and insomnia, but none discontinued treatment because of side effects. Results highlighted the potential role of this treatment in the management of IPF. This study was excluded because it did not compare oral or inhaled corticosteroids to placebo.

[Douglas 2000](#) and co-workers retrospectively assessed the impact of different interventions on survival in participants affected by IPF. Inclusion criteria were similar to ATS 2000 criteria (ATS 2000). Treatment groups were as follows: no treatment in 157 (32.2%), prednisone only in 54 (11.1%), colchicine in 167 (34.3%), colchicine plus prednisone in 71 (14.6%), other programs in 38 (7.8%); oxygen therapy was recommended in 133 participants (27.7%). Colchicine was used at a dose of 0.6 mg once or twice daily. Prednisone dosage was tapered to maintenance dose of 5 to 40 mg/day. By univariate analysis, no significant difference was found when survival was compared across all recommended treatments groups simultaneously, while a worse survival was associated with prednisone only or colchicine plus prednisone therapy compared with no therapy and with oxygen therapy compared with no oxygen therapy. On multivariate analysis, worse survival was associated with older age, male gender, lower DLCO, lower alveolar volume and a history of worsening pulmonary function. After adjustment for these variables, no evidence indicated that survival was associated with the recommended treatment or with oxygen therapy. Authors concluded that the different treatments did not show any significant effect compared with no therapy. This study was excluded because it was not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.

[Noth I and Martinez FJ](#) reviewed IPF treatment concluding that some patients may benefit from corticosteroids therapy. However, they also stressed that the effect of steroid therapy cannot

be precisely defined without data from randomised, placebo-controlled studies.

[Hospenthal MAC](#) reviewed recent advances in diagnosis and management of IPF and reached the same conclusions that, although non definitive medical treatment is available, most patients are still given trials of corticosteroids, alone or in combination with cytotoxic agents. However, this therapeutic approach has no been shown to modify patient survival, and lung transplantation represent the only effective therapeutic strategy.

Risk of bias in included studies

We did not retrieve any RCTs or CCTs comparing the active treatment (corticosteroid therapy) with a placebo arm. Therefore, we could not judge the quality of included studies.

Effects of interventions

No RCTs or CCTs comparing corticosteroid treatment with placebo for the therapy of IPF have been published. Therefore, any conclusive evidence supporting the use of corticosteroid therapy for the treatment of IPF is missing. When considering the sporadic results showing a beneficial effect of corticosteroid therapy in some IPF patients coming from non controlled studies the difference in diagnostic criteria for patients included in the studies should be carefully considered. In particular, the recent classification of the disease based upon histologic pattern [ATS 2002](#) precisely defines the entity to which the term IPF should be applied, separating this from other diseases (such as NSIP) which are more responsive to steroids and which were possibly included in older studies.

DISCUSSION

Since no placebo-controlled trials analysing the efficacy of corticosteroid therapy in patients with IPF/UIP have been published, at the moment there is no evidence to support the efficacy of corticosteroids in the treatment of IPF. Therefore, it is crucial to make an accurate diagnosis of IPF/UIP and to exclude other, diseases potentially steroid-responsive. In this context, the ATS diagnostic criteria [ATS 2002](#), including an adequate histological biopsy when necessary, should be considered as the mainstay of diagnosis.

In some cases a definite biopsy-proven diagnosis of IPF cannot be achieved and the use of corticosteroids in such patients with a suggestive clinical and radiological picture but without confirmatory histologic evidence can be considered, with the aim of ruling out a disorder with another histologic pattern (e.g. NSIP). A positive clinical response in this setting may be indicative of the presence of another disorder. The well-established and potentially serious side-effects of oral corticosteroid therapy need to be taken into account when considering this approach.

Therefore, the use of systemic corticosteroid could be considered in cases where the diagnosis of IPF/UIP has not been definitely achieved.

Given the considerable recent advances in the understanding of the pathogenetic factors involved in IPF/UIP, the use of anti-inflammatory drugs (such as corticosteroids) does not seem to be justified.

AUTHORS' CONCLUSIONS

Implications for practice

For patients with a definite diagnosis of IPF/UIP there is no evidence that corticosteroid therapy modifies the natural history of the disease.

Implications for research

Most recent advances on IPF pathogenesis do not support the design of randomized or controlled clinical trials investigating the efficacy systemic corticosteroids in IPF patients.

ACKNOWLEDGEMENTS

Karen Blackhall, Toby Lasserson and Liz Arnold are acknowledged for their evaluable help in retrieval of references and helpful advice.

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CHARACTERISTICS OF STUDIES

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Behera 1998	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Douglas 1997	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Douglas 1998	It involves drugs (colchicine) other than oral or inhaled corticosteroids.
Douglas 2000	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Gay 1998	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Gulsvik 1986	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Hanson 1995	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Hospenthal MAC	Not a RCT or CCT: review with no original data.
Johnson 1989	It involves drugs (cyclophosphamide) other than oral or inhaled corticosteroids.
Kang 1999	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Keogh 1983	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Noth I and Martinez FJ	Not a RCT or CCT: review with no original data.
O'Donnell 1987	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Raghu 1991	It involves drugs (azathioprine) other than oral or inhaled corticosteroids.
Selman 1998	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Turner-Warwick 1980	Not a RCT or a CCT comparing oral or inhaled corticosteroids to placebo.
Ziesche 1999	It involves drugs (interferon gamma-1b) other than oral or inhaled corticosteroids.

APPENDICES

Appendix 1. MEDLINE search strategy

1. exp Lung Diseases, Interstitial/
2. (pulmonary adj3 fibros\$).mp.
3. (Interstitial adj5 pneumonia\$).mp.
4. alveoliti\$.mp.
5. (Interstitial adj5 lung disease\$).mp.
6. 1 or 2 or 3 or 4 or 5
7. exp Adrenal Cortex Hormones/
8. (Adrenal cortex hormone\$ or steroid\$ or corticosteroid\$ or glucocorticoid\$ or corticoid\$).mp.
9. 7 or 8
10. 6 and 9

(This search was combined with an RCT filter as outlined in the [Airways Group editorial information](#) on the Cochrane Library)

Appendix 2. EMBASE search strategy

1. exp INTERSTITIAL LUNG DISEASE/
2. (pulmonary adj3 fibros\$).mp.
3. (Interstitial adj5 pneumonia\$).mp.
4. (interstitial adj3 lung disease\$).mp.
5. alveoliti\$.mp.
6. 1 or 2 or 3 or 4 or 5
7. exp CORTICOSTEROID THERAPY/
8. (Adrenal cortex hormone\$ or steroid\$ or corticosteroid\$ or glucocorticoid\$ or corticoid\$).mp.
9. 7 or 8
10. 6 and 9

(This search was combined with an RCT filter as outlined in the [Airways Group editorial information](#) on the Cochrane Library)

Appendix 3. CENTRAL search strategy

- #1 MeSH descriptor Lung Diseases, Interstitial explode all trees in MeSH products
- #2 (pulmonary near fibros*) in All Fields in all products
- #3 (interstitial near pneumonia*) in All Fields in all products
- #4 (interstitial* near lung* near disease*) in All Fields in all products
- #5 (#1 OR #2 OR #3 OR #4)
- #6 MeSH descriptor Adrenal Cortex Hormones explode all trees in MeSH products
- #7 "adrenal cortex hormone*" or steroid* or corticosteroid* or glucocorticoid* or corticoid* in All Fields in all products
- #8 beclomethasone or budesonide or fluticasone or flunisolide or triamcinolone or ciclesonide in All Fields in all products
- #9 (#6 OR #7 OR #8)
- #10 (#5 AND #9)

WHAT'S NEW

Date	Event	Description
1 December 2009	Amended	Contact details amended

HISTORY

Protocol first published: Issue 1, 2001

Review first published: Issue 3, 2003

Date	Event	Description
24 June 2008	New search has been performed	Literature search re-run; no new studies were identified.
26 March 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

L Richeldi and HR Davies designed the clinical question behind the review, evaluated all retrieved references, selected those potentially eligible for meta-analysis, evaluated evidence grading and wrote the review. P Spagnolo and F Luppi helped with literature search and with grading of the retrieved references.

DECLARATIONS OF INTEREST

None

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Garfield Weston Foundation, UK.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenal Cortex Hormones [*therapeutic use]; Pulmonary Fibrosis [*drug therapy]

MeSH check words

Adult; Humans