Long term effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a meta-analysis


Authors' objectives
To answer the question 'Are inhaled corticosteroids able to slow down the decline in lung function (forced expiratory volume in 1 second, FEV1) in chronic obstructive pulmonary disease (COPD)?'

Searching
The following electronic databases were searched: MEDLINE from 1983 to 1996; BIOSIS Previews from 1991 to 1996; On Line Contents from 1993 to 1996; Grey Literature in the Netherlands ('GLIN') from 1982 to 1996; the Cochrane Library; and EMBASE from 1993 to 1996. A free text strategy was used using keywords listed in the paper. The references lists of the retrieved papers were also examined.

Study selection
Study designs of evaluations included in the review
Only randomised, placebo-controlled trials with a duration of at least 24 months were eligible for inclusion in the review.

Specific interventions included in the review
Studies of any inhaled corticosteroids were eligible for inclusion in the review. The included studies covered budesonide (800 microg twice daily) metered-dose inhaler (MDI) through a Nebuhaler, beclomethasone (1,500 microg) MDI, and beclomethasone (800 microg) MDI plus terbutaline (2 mg). Budesonide was compared with budesonide plus prednisone; beclomethasone was compared with placebo; and terbutaline plus beclomethasone was compared with terbutaline plus imipramine and terbutaline alone (considered to be beclomethasone versus imipramine versus placebo for the purposes of the meta-analysis; furthermore, the imipramine was considered to be placebo also).

Participants included in the review
Only patients with a strict diagnosis of COPD, i.e. chronic breathlessness, especially upon exertion and/or productive cough during more than 3 months/year in two successive years, were eligible for inclusion in the review. In addition, the patients had to be aged at least 40 years; have a FEV1 after treatment with a beta-agonist of at least the predicted FEV1 minus 1.64 standard deviations; have a bronchodilator response to a beta-agonist of at least 9% of the predicted FEV1; and to be a previous or current smoker. Of the three included studies, one was of patients aged under 70 years, one was of patients 75 years or under, and one was of patients aged 18 to 60 years.

Outcomes assessed in the review
The primary efficacy parameter for the meta-analysis was pre-bronchodilator decline in FEV1, measured at two- or three-monthly intervals. The secondary efficacy parameters were post-bronchodilator decline in FEV1, the number of drop-outs and the number of exacerbations. Only data up to 24 months were used.

How were decisions on the relevance of primary studies made?
The selection criteria were applied to published reports and then the databases for all potentially eligible studies were collected. The number of reviewers involved was not reported.

Assessment of study quality
The individual patients within the included studies were checked for inclusion in the meta-analysis against the inclusion criteria specified for the review. In addition, the number of drop-outs and the reason for drop-out were recorded. Baseline and follow-up data were sent to the trial investigators for verification. The individual patient data (IPD) were checked against the selection criteria for the meta-analysis. The actual methods used were not described. It was not
Data extraction
The protocols and databases of the three included studies were collected. The categories of data extracted were: bibliographic details; inclusion criteria; exclusion criteria; setting; design; duration of study; study drugs; concomitant drugs; outcome; criteria for pulmonary drop-out; definition of exacerbation used; treatment of exacerbation; method of allergy measurement; details of statistical analysis; and characteristics and outcomes for individual patients. The investigators of the studies were sent an output of the baseline characteristics and follow-up data of their own study, in order to avoid misinterpretation of their study data.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis of IPD. Differences between the oral corticosteroid and placebo, in terms of the drop-out rates and the number of exacerbations per year, were tested using a chi-squared test and Student’s t-test, respectively. Using a random coefficient model, all available time points of FEV1 measurements were incorporated and analysed. The first analysis was versus placebo, while a second analysis compared ‘low dose’ versus ‘high dose’. Factors such as age, FEV1, smoking, the number of exacerbations, and so on, were included in the model to correct for possible confounders and also to enable an assessment of which characteristics may predict the influence of treatment on the change in FEV1. First, all possible interaction terms of the independent variables with treatment were incorporated into the model. Second, in a backwards procedure, variables with the highest p-value were subsequently deleted until only variables with a p-value of less than 0.05 remained.

How were differences between studies investigated?
The authors do not report testing for between-study differences. They reduced the differences between the included studies by including only those patients and treatments that fitted their selection criteria for the meta-analysis. All patients included in the analysis appear to have been treated as if they came from a single trial.

Results of the review
Three studies were included in the review. The total number of patients in these studies was 303, but only 197 met the criteria for inclusion in the meta-analysis.

The estimated 2-year difference in pre-bronchodilator FEV1 was 0.034 L/year (95% confidence interval, CI: 0.005, 0.063) in the inhaled corticosteroid group, compared with placebo. The post-bronchodilator FEV1 showed a difference of +0.039 L/year (95% CI: -0.006, 0.084). No beneficial effect was seen on exacerbation rate. Drop-outs due to a worsening of the disease were higher in the placebo group (9 out of 88) than in the inhaled corticosteroid group (4 out of 95) (p=0.11).

Authors’ conclusions
This study of a group of patients with strictly defined moderate to severe COPD showed a preservation of the FEV1 during two years of treatment with relatively high dosages of inhaled corticosteroids (1,500 microg beclomethasone or 1,600 microg budesonide daily).

CRD commentary
This review addressed a clear question relevant to clinical practice and used clearly defined inclusion criteria. It was not completely clear from the paper why a study of terbutaline was included, or to what extent the use of a beta-agonist in that study differed from its use in the other included studies. The search for relevant studies appears to have been comprehensive, in terms of electronic databases, but no attempts to contact or involve the primary study investigators prior to study selection appear to have been made. The validity of the study designs was not checked, and it is unclear from the paper how much effort was made to check the IPD. The details of the primary studies and the summarised IPD were well presented in the paper. The methods employed to pool the IPD appear to have ignored the randomisation
within the primary studies, which is not appropriate.

The authors’ conclusions appear to be supported by the review. However, given the small number of patients included in the meta-analysis, these findings should be taken as preliminary.

**Implications of the review for practice and research**

The authors did not state any implications for further research and practice.

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