Oral corticosteroid trials in the management of stable chronic obstructive pulmonary disease

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Summary

Although recent guidelines for managing chronic obstructive pulmonary disease (COPD) recommend a trial of oral corticosteroids in the initial assessment, its prognostic value remains unclear. We prospectively studied 127 adults (64% men) with stable COPD (FEV₁/FVC < 60%) over 1 year. At entry, we measured lung volumes, gas transfer factor, respiratory symptoms (by questionnaire), and peripheral blood eosinophil count. Skin-prick testing was done, and spirometry after nebulized 5 mg salbutamol and, after 2 weeks, oral prednisolone. Physician A gave all patients inhaled beclomethasone dipropionate (800 mcg/day), whereas physician B prescribed this only to those with a positive oral corticosteroid trial. At 1 year, spirometry and respiratory questionnaire were repeated, with an estimate of overall symptom severity on a visual analogue scale. Follow-up data were available in 104 (82%) patients. Of these, 32 (31%) were unresponsive to salbutamol and prednisolone; 48 (46%) were responsive to beta agonists but not to corticosteroids, and 24 (23%) responded to corticosteroids and salbutamol. Patients in all groups were comparable, except that the prednisolone responders had a higher mean eosinophil count ($p < 0.001$) and more were ex-smokers ($p < 0.001$). Only the response to oral prednisolone correlated with the change in pre-bronchodilator FEV₁ over 1 year. Oral prednisolone responders had higher FEV₁ at 1 year ($p < 0.02$) and significantly lower symptom scores ($p < 0.02$). In all patients inhaled beclomethasone dipropionate COPD, corticosteroid trials contribute information additional to that gained from nebulized bronchodilator reversibility testing. Patients with a positive response to a corticosteroid trial are more likely to have improved symptomatically and spirometrically at 1 year.

Introduction

Chronic obstructive pulmonary disease (COPD) is an important cause of morbidity and mortality in the USA and elsewhere. Symptomatic bronchodilator therapy is a cornerstone of COPD management, and an objective assessment of this treatment is recommended in all patients. In contrast, the role of corticosteroids orally or by inhalation remains contentious. One large meta-analysis estimated that 10% of stable COPD patients responded to a 2-week oral corticosteroid trial. Retrospective studies of COPD patients taking oral prednisolone suggest that some patients show initial improvement in lung function and a reduction in the subsequent rate of decline. Bronchodilator response is not particularly sensitive in identifying such patients. In a study of patients with COPD, lung function improved modestly over a 1-year period in those treated with inhaled corticosteroids. It is not known if such responses can be predicted, nor even whether they can be expected, in more severe COPD.

We have previously shown that almost 40% of patients with stable moderate and severe COPD have a bronchodilator response to a two-week trial of corticosteroids. However, it was not possible to...
differentiate oral corticosteroid responders from non-responders at presentation, since the two groups of patients presented with similar symptoms, suggesting that the ‘responsive’ patients were not merely a subgroup of asthmatics. The aim of this study was to investigate if patients with stable moderate-to-severe COPD who have an improvement in spirometry after a steroid trial and are subsequently treated with inhaled steroids have improved lung function and improved symptoms after 1 year follow-up, compared to non-responders.

**Methods**

**Patients**

Participants in this study were drawn from an initial cohort of 127 patients previously described, who met the ATS definition of COPD and had been seen consecutively as new referrals to our out-patient department. All had clinically stable COPD, defined by a history of progressive continuous breathlessness of at least 1 year duration and documented airflow limitation (FEV₁/FVC < 60%). Patients with cardiac or other pulmonary disorders, including documented asthma, were excluded. Asthma was excluded on the basis of symptoms of intermittent wheeze and breathlessness, history of atopy or previous physician diagnosis. None of the patients had an acute exacerbation or received oral corticosteroids within 3 months of assessment. Those entering this study had been taking ≤ 200 mcg beclomethasone or equivalent, and/or had used this for less than 1 month before assessment and/or had not complied with their treatment.

Each patient attended the laboratory three times, and was asked to omit inhaled bronchodilators for 6 h and oral bronchodilators for 24 h beforehand. At the first visit, a respiratory symptom questionnaire was administered and a subjective assessment of overall symptom severity was recorded on a 10 cm visual analogue scale (VAS). Spirometry before and after 5 mg nebulized salbutamol was also performed. Helium dilution lung volumes and carbon monoxide transfer factor were measured before the bronchodilator test, and skin prick tests to five common allergens and an eosinophil count were done. The patient was prescribed a 2-week course of oral prednisolone, 30 mg per day, and returned for a further prebronchodilator FEV₁ at its conclusion.

The results of both types of reversibility testing were available to the referring physicians. The patients were referred by one of two physicians and allocated in a random order to the laboratory staff, who performed the tests without knowledge of their source. The referring physicians adopted different policies in response to the results. Both advised that patients with a positive corticosteroid trial received inhaled beclomethasone dipropionate through a metered dose inhaler (with or without a spacer, depending upon the ability of the patient to use the MDI appropriately) as 800 mcg daily in divided doses. Physician A’s policy was to give the same treatment to all other patients irrespective of their bronchodilator responses, whilst physician B restricted inhaled corticosteroid treatment to those with a positive corticosteroid trial. Patients were reviewed 3-monthly, when smoking cessation and compliance with treatment were encouraged and inhaler technique was checked.

All patients were invited to return for visit 3 at 1 year after their initial assessment when the questionnaire and salbutamol reversibility test were repeated. The corticosteroid challenge was not repeated. Patients were asked the same questions on the presence or absence of symptoms such as cough and sputum, and on treatment actually taken, and a VAS of symptom severity was repeated. Medical staff recording the data were unaware of the results of the initial investigations. Each patient gave informed consent to the study, which was approved by the hospital ethical committee.

All spirometric assessments were performed on the same water spirometer (PK Morgan, Rainham, Kent). The staff collecting the data were unaware of the patients’ physician, initial spirometry or subsequent treatment. The best FEV₁ and FVC from three technically acceptable tracings were recorded. The salbutamol was nebulized using a System 22 nebulizer powered by oxygen at 5 l/s. Post bronchodilator measurements were recorded 15 min after the nebulization ended.

A significant change in lung function was defined as a change in FEV₁ that was both 15% or more of the baseline value and greater or equal to 200 ml. This allows for the spontaneous variability of the FEV₁ between repeated measurements and encompasses both the European Respiratory Society’s and American Thoracic Society’s criteria for a bronchodilator response.

**Statistical analysis**

Statistical comparisons between group data were made using ANOVA for normally distributed data or else by non-parametric Wilcoxon rank sum tests. To make allowance for the use of multiple comparisons, we used the Bonferroni correction. As our study did not contain an initial control group, we calculated a treatment effect size using the method suggested by Kazis and the formula: effect size = (X2 - X1)/SD, where X2 is the mean post-bronchodilator FEV₁ value and X1 the mean pre-bronchodilator value. The
steroids. The remaining 13 were contacted but showed a smaller initial change with prednisolone below 1 l.

The anthropomorphic and physiological characteristics of the non-attenders did not differ significantly from the parent group. The pre- and post-bronchodilator FEV\(_1\) at visit 1 was closely related to that at visit 3 (r = 0.72 and 0.79, respectively). The variance of the data around the mean was not significantly different for either pre- or post-bronchodilator values. The mean FEV\(_1\) rose over the year from 0.96 (0.40) to 1.07 (0.53) l (p < 0.01).

Follow-up data at visit 3 were available in 104 (82%) of the original 127 patients, and all subsequent data relate to these patients. Of the 23 not followed-up, three had died, five had moved away from the area, and two were on regular maintenance oral corticosteroids. The remaining 13 were contacted but declined to attend. Of these 127 patients, 64% were male and 93% had smoked cigarettes. The mean FEV\(_1\) was 0.92 (0.32) l with 63% having an FEV\(_1\) below 1 l. The anthropomorphic and physiological characteristics of the non-attenders did not differ significantly from the parent group. The pre- and post-bronchodilator FEV\(_1\) at visit 1 was closely related to that at visit 3 (r = 0.72 and 0.79, respectively). The variance of the data around the mean was not significantly different for either pre- or post-bronchodilator values. The mean FEV\(_1\) rose over the year from 0.96 (0.40) to 1.07 (0.53) l (p < 0.01).

Patients were divisible into three groups by bronchodilator response. Thirty-two (31%) were unresponsive to salbutamol at either visits 1 or 3 and to prednisolone at visit 1 (group 1). Forty-eight (46%) were corticosteroid-unresponsive but salbutamol-responsive (group 2). Twenty-four (23%) had a positive bronchodilator response to corticosteroids and also had a bronchodilator response to salbutamol (group 3).

The characteristics of these patients at study entry are shown in Table 1. The steroid responders had a higher mean eosinophil count (p < 0.0001), were more likely to be ex-smokers (p < 0.0001) and had a significantly higher DLCO (p < 0.001). The changes in symptoms, lung function and drug therapy over the 1-year period are summarized in Table 2. These will be considered for each group in turn.

Symptoms, spirometry and bronchodilator reversibility were unchanged over the year despite bronchodilator-unresponsive patients receiving more treatment (group 1, Table 2). Similarly, symptoms and spirometry (either before or after bronchodilator) did not change over the year in the corticosteroids-unresponsive but bronchodilator-responsive patients (group 2, Table 2). Thirty-five of the 80 patients in groups 1 and 2 were treated with inhaled corticosteroids over the period between visit 2 and visit 3.

There were no differences in spirometry and symptoms between these two groups.

Over the year, group mean FEV\(_1\) rose from 0.88 (0.26) to 1.29 (0.58) l in the corticosteroid and bronchodilator responsive patients (group 3, Table 2). The larger the initial response to prednisolone, the greater was the chance that the baseline FEV\(_1\) would be higher at 1 year; especially in subjects whose initial change in FEV\(_1\) after an oral corticosteroid trial was at least 400 ml (Figure 1). In four patients the FEV\(_1\) at 1 year was equivalent to that after their initial course of oral prednisolone, and these patients showed no further bronchodilation with beta agonists. Eighteen patients still showed significant increases in FEV\(_1\) after beta agonist at 1 year (mean initial change 0.57 l; mean change at 1 year 0.42 l). The remaining six patients, (mean FEV\(_1\) 0.88 l (0.18)) showed a smaller initial change with prednisolone (mean change in FEV\(_1\) 0.46 vs. 0.87 l; p < 0.05) and a smaller increase in baseline FEV\(_1\) at 1 year (FEV\(_1\) 0.88 (0.18) l initially; 1.18 (0.32) l at follow-up).

Only patients whose baseline FEV\(_1\) improved reported an improvement in symptoms over the year (Figure 2).

**Predictors of symptoms and FEV\(_1\) at 1 year**

The percentage of patients complaining of cough, sputum production and wheeze did not differ between the physiologically-defined groups or within each group over the year of follow-up. The presence of specific clinical features, e.g. sputum production, wheeze, or laboratory findings, e.g. atopy, blood eosinophilia, did not accurately predict those patients whose baseline or post-bronchodilator FEV\(_1\) subsequently improved. This was true irrespective of the physician managing the patient. Likewise, the change in FEV\(_1\) after nebulized salbutamol was unhelpful, but the response to two weeks oral prednisolone was correlated with subsequent baseline FEV\(_1\) (Spearman coefficient; r = 0.60, p < 0.01) (Figure 3a, b).

The effect size for changes in baseline FEV\(_1\) for the whole group was 0.28 using the pre-bronchodilator FEV\(_1\) and 0.15 using the post-bronchodilator FEV\(_1\). This change was due almost entirely to patients in group 3 who had shown an initial positive oral corticosteroid trial.

**Discussion**

The purpose of this study was to assess the long-term value, if any, of FEV\(_1\) response to an oral corticosteroid trial in patients with moderate and severe stable COPD. The results of our study indicate that a subset of patients with stable COPD who have
Table 1  Clinical, immunological and lung function data at study entry

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Group 1 (n = 32)</th>
<th>Group 2 (n = 48)</th>
<th>Group 3 (n = 24)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>59 (7)</td>
<td>61 (8)</td>
<td>62 (8)</td>
<td>NS</td>
</tr>
<tr>
<td>No. (%) male</td>
<td>18 (56)</td>
<td>31 (65)</td>
<td>17 (71)</td>
<td>NS</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>44</td>
<td>38</td>
<td>17</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pack-years smoked</td>
<td>30 (17)</td>
<td>36 (25)</td>
<td>30 (21)</td>
<td>NS</td>
</tr>
<tr>
<td>Skin test positive (%)</td>
<td>41</td>
<td>42</td>
<td>46</td>
<td>NS</td>
</tr>
<tr>
<td>Eosinophils × 10⁹/l</td>
<td>127 (42)</td>
<td>231 (72)</td>
<td>416 (92)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>FEV₁ (% predicted)</td>
<td>39 (19)</td>
<td>35 (14)</td>
<td>32 (12)</td>
<td>NS</td>
</tr>
<tr>
<td>RV (l)</td>
<td>2.9 (0.6)</td>
<td>3.6 (1.0)</td>
<td>3.4 (1.3)</td>
<td>NS</td>
</tr>
<tr>
<td>TLC (l)</td>
<td>5.1 (1.1)</td>
<td>5.8 (1.2)</td>
<td>5.5 (1.4)</td>
<td>NS</td>
</tr>
<tr>
<td>DLCO (ml/min/kPa)</td>
<td>5.96 (1.77)</td>
<td>6.73 (2.60)</td>
<td>6.93 (3.03)</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
</table>

*p values refer to significant differences between group 3 and group 1, except *refers to differences between group 1 and groups 2 and 3.

Table 2  Spirometric data, symptoms, smoking status and drug treatment at study entry and at 1 year

<table>
<thead>
<tr>
<th>Patient characteristic</th>
<th>Group 1 (n = 32)</th>
<th>Group 2 (n = 48)</th>
<th>Group 3 (n = 24)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>1 year</td>
<td>Initial</td>
</tr>
<tr>
<td>Pre-bronchodilator FEV₁ (l)</td>
<td>1.03 (0.52)</td>
<td>1.13 (0.65)</td>
<td>0.94 (0.37)</td>
</tr>
<tr>
<td>ΔFEV₁ post 5 mg nebulized salbutamol (1)</td>
<td>0.02 (0.12)</td>
<td>0.02 (0.15)</td>
<td>0.24 (0.15)</td>
</tr>
<tr>
<td>ΔFEV₁ post oral corticosteroid trial (1)</td>
<td>0.05 (0.09)</td>
<td>0.01 (0.16)</td>
<td>0.77 (0.52)</td>
</tr>
<tr>
<td>Dyspnoea grade</td>
<td>3.3 (1.5)</td>
<td>3.8 (1.4)</td>
<td>3.6 (1.2)</td>
</tr>
<tr>
<td>Symptom VAS</td>
<td>5.6 (1.8)</td>
<td>5.3 (1.7)</td>
<td>5.6 (1.8)</td>
</tr>
<tr>
<td>Current smokers (%)</td>
<td>44</td>
<td>19</td>
<td>38</td>
</tr>
</tbody>
</table>

Dyspnoea was assessed with the Fletcher (MRC) dyspnea scale, overall symptom score by a visual analogue scale (VAS). Data are means (SD). *Significant difference (p < 0.02) within a group over the 1 year follow-up.

Figure 1. Change in prebronchodilator FEV₁ over 1 year vs. change in FEV₁ after 2 weeks prednisolone in those patients with a positive oral corticosteroid trial.

Figure 2. Relationship of change in FEV₁ and change in VAS symptom score over one year in the three groups of patients (graph shows mean scores with standard error bars).

Figure 1. Change in prebronchodilator FEV₁ over 1 year vs. change in FEV₁ after 2 weeks prednisolone in those patients with a positive oral corticosteroid trial.

Figure 2. Relationship of change in FEV₁ and change in VAS symptom score over one year in the three groups of patients (graph shows mean scores with standard error bars).

an improvement in spirometry after a trial of oral corticosteroids, when subsequently treated with inhaled corticosteroids have an improved clinical course and improved lung function. Our results also suggest that patients with COPD have a variable response to high-dose inhaled beta agonists over time, and that the presence of a bronchodilator response in these patients does not indicate better lung function or symptoms at 1 year follow-up.

This study followed carefully-defined consecutive
Managing COPD

The existence of a corticosteroid- and bronchodilator-responsive subset in COPD has some theoretical support. Recent biopsy studies have confirmed the presence of inflammatory cell infiltrates including T lymphocytes in bronchial biopsies from COPD patients. Amongst COPD patients with equivalent reductions in FEV₁, those with relatively less emphysema had more eosinophils in their airways and had exhibited greater bronchodilator responses during life. The physiological course of our corticosteroid-responsive group is compatible with some, or all, of the above processes.

We tested with a higher dose of beta agonist than in the IPPB study to ensure that we were high on the plateau of the dose-response relationships for bronchodilators. Previously we have found little difference between beta agonists and ipratropium in defining a bronchodilator response at these concentrations. We deliberately chose a wide range of bronchodilator responses as an entry criteria, unlike either of the current prospective trials of inhaled corticosteroids in COPD (EUROSCOP/ISOLDE), as our study was a clinical one and we did not wish to censor our data. The absence of a placebo/corticosteroid trial has limited the conclusions we can draw, but such studies cannot easily be applied to patient care as they have a cross-over and order effect.

We used FEV₁ as our principal outcome measure because of its reproducibility. Changes in smoking and treatment had little effect on the course of the illness. This could reflect different susceptibility, the relatively small numbers in each group, or the duration of follow-up. Although the study size is comparatively small, the results of this study also seem to suggest that only those patients with a positive oral corticosteroid response have a sustained improvement in pulmonary function.
compared to non-responders subsequently treated with inhaled steroids. The absence of improvement in those oral corticosteroid non-responders treated with inhaled corticosteroids is disappointing. It is possible that this reflects an inherently different natural history as suggested by Burrows\textsuperscript{22} or simply a spectrum of disease response with higher/longer dosage with inhaled corticosteroids being needed to produce an improvement. This point may be clarified when the EUROSCOP and ISOLDE studies are published.

The results of this study suggest that patients with positive corticosteroid trials do appear to behave differently from other COPD patients in terms of FEV\textsubscript{1} and symptoms. In this study we have shown that an FEV\textsubscript{1} response to oral corticosteroids, but not beta agonists, yields prognostically useful information. Furthermore, our data support the BTS guidelines that suggest that a trial of oral prednisolone is clinically useful in stable COPD patients. However, the interpretation of individual corticosteroid responses is likely to remain difficult given the uncertainties about the reproducibility of this measurement. When we used a change of approximately 2 SD of the FEV\textsubscript{1} measurement (400 ml) to define a responder, most individuals showed improvements at 1 year, but even this was not entirely specific. Further information about the biological basis of response to corticosteroids is needed to explain this heterogeneity.

References


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10. Tweedale PM, Alexander F, McHardy GJR. Short term variability in FEV\textsubscript{1} and bronchodilator responsiveness in patients with obstructive ventilatory defects. \textit{Thorax} 1987; \textbf{42}:487–90.


14. Burrows B, Bloom JW, Traver GA, Clive MG. The cause and measurement (400 ml) to define a responder, most individuals showed improvements at 1 year, but even this was not entirely specific. Further information about the biological basis of response to corticosteroids is needed to explain this heterogeneity.

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