Inflammation in chronic obstructive pulmonary disease: its assessment and the effects of corticosteroids
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Chapter 2

Long term effects of budesonide on inflammatory status in COPD

Martin Boorsma\textsuperscript{1}
René Lutter\textsuperscript{1,2}
Marianne A. van de Pol\textsuperscript{2}
Theo A. Out\textsuperscript{2}
Henk M. Jansen\textsuperscript{1}
René E. Jonkers\textsuperscript{1}

\textsuperscript{1}Department of Pulmonology and \textsuperscript{2}Department of Experimental Immunology, Academic Medical Center, Amsterdam

Abstract

A beneficial effect of long-term corticosteroid treatment in patients with COPD may be linked to suppressing inflammation, in particular neutrophilic inflammation.

Effects on neutrophilic and eosinophilic inflammation and on lung function of long-term inhaled budesonide treatment (800 μg daily, 6 months, double-blind, randomised, cross-over versus placebo) were studied and compared to the effects of 3 weeks oral prednisolone (30 mg daily) in 19 patients with COPD (mean age 63 y, FEV₁ 65% of predicted).

Neither treatment influenced neutrophilic inflammation. Inhaled budesonide compared to placebo significantly reduced sputum % eosinophils at 3 months (-42%, p=0.036), but not significantly at 6 months (-31%, p=0.78). Eosinophil count per g sputum was decreased with 30% at 3 months (p=0.09) and with 9% at 6 months (p=0.78). FEV₁ was slightly higher after 6 months budesonide (+2.5% predicted, p=0.09). Prednisolone significantly reduced sputum % eosinophils (-87%, p=0.007), but did not affect eosinophil count per g sputum and did not improve FEV₁ (-0.6% predicted, p=0.40).

A higher baseline FEV₁ (%) correlated with effects of budesonide on FEV₁ (p<0.001), effects on sputum interleukin-8 and eosinophil cationic protein (both p<0.05) and tended to correlate with effects on sputum % eosinophils (p=0.056). Baseline inflammatory data and effects of prednisolone did not correlate with effects of budesonide.

Effects of inhaled budesonide in COPD are not restricted to patients with severe disease and may be linked to a suppression of eosinophilic inflammation. Investigating effects of prednisolone has no predictive value for long-term treatment.
**Introduction**

Chronic obstructive pulmonary disease (COPD) is probably a heterogeneous complex of different disease entities that are characterized by airway inflammation and lead to progressive and irreversible airway obstruction.\(^1\) Inhaled corticosteroids are expected to suppress this inflammation and are prescribed to many COPD patients, especially those with severe airflow limitation or showing frequent exacerbations.\(^2\) This is based upon results obtained in large-scale clinical studies.\(^3\)\(^5\) The effect of corticosteroids may be related to the transient sputum eosinophilia during COPD exacerbations,\(^6\)\(^7\) and the suppressive effects of corticosteroids on eosinophilic inflammation in general, such as in asthma.\(^8\) However, the most prominent inflammatory cell in the airway lumen of COPD patients in stable disease is the neutrophilic granulocyte, the increased presence of which in the airways is associated with enhanced loss of lung function.\(^9\) Though neutrophilic inflammation is considered to be rather unresponsive to corticosteroid treatment, a small effect of long-term treatment with inhaled corticosteroids on the progressive decrease in lung function has been substantiated.\(^10\)

Several small-scale short-term studies and a recent meta-analysis showed an effect of inhaled corticosteroids on sputum neutrophilia or sputum eosinophilia.\(^11\)-\(^13\). The heterogeneous effects of inhaled corticosteroids on COPD, observed in different studies are likely related to heterogeneity in patient selection and hereby to heterogeneity in inflammation.

The primary aim of the present study was to document the effect of long-term inhaled corticosteroid treatment on neutrophilic and eosinophilic inflammation in COPD patients and additionally whether these effects can be predicted by documenting the anti-inflammatory effects of a short course of oral prednisolone. Although previous studies showed that assessing the effects of a short course with a systemic corticosteroid could not be used as a predictor of clinical effects of long-term treatment with inhaled corticosteroids on lung function in individual patients,\(^14\) this may be different for inflammatory parameters. A secondary aim was studying the impact of the severity of airflow limitation as a clinical predictor of the anti-inflammatory effects. Based on the effect on exacerbation frequency being most prominent in the more severely affected patients one might expect the most outspoken anti-inflammatory effects to occur in this patient group as well.
Methods

Subjects

Patients had clinically stable, smoking-related COPD. At enrolment, patients were aged > 45, had > 15 Pack-Years, a pre-bronchodilator FEV₁ > 1.0 L and > 30% of predicted, a post-bronchodilator FEV₁/VC < 0.70 and reversibility < 12% of predicted. Excluded were patients with a history of asthma, allergy, a positive blood RAST test for common aero-allergens or α-1-antitrypsin deficiency. Written informed consent was obtained; the study was conducted according to the declaration of Helsinki after approval by the local medical ethics committee.

Study design

The study (Figure 1) consisted of a run-in period of 8 weeks, a prednisolone treatment period of 3 weeks (30 mg once daily), a wash-out period of 3 weeks and two randomised, cross-over, double-blind, inhaled treatment periods of 6 months each with 400 μg budesonide or placebo twice daily (Pulmicort® Turbuhaler®, AstraZeneca). Lung function (spirometry and body box measurements, before and after β₂) was assessed, a blood sample was drawn for standard haematology and clinical chemistry and induced sputum was collected before and after each period and halfway inhaled treatment periods.

<table>
<thead>
<tr>
<th>run-in</th>
<th>prednisolone</th>
<th>wash-out</th>
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<td>budesonide</td>
<td>placebo</td>
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<td>53</td>
<td>17</td>
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<td>66</td>
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Figure 1. Study design. Inhaled budesonide and placebo were given in a double blind, randomised, cross-over fashion. The number of patients at the different stages in the study is shown.

Sputum induction and analysis of sputum parameters.

After β₂-agonist inhalation, sputum was induced by hypertonic saline (3 consecutive periods of 5 minutes inhalation with 3%, 4% and 5% saline respectively). Whole sputum was liquefied with dithiotreitol. Differential cell counts were performed on minimally 500 non-squamous cells, samples with > 80% squamous cells were excluded from statistical analyses. Soluble inflammatory markers consisted of myeloperoxidase (MPO), interleukin (IL)-8, eosinophil cationic protein (ECP). Respiratory membrane permeability was estimated from levels of alpha-2-macroglobulin and albumin in sputum.
Data analysis

Data obtained at the end of the exacerbation-free and glucocorticosteroid-free run-in period was defined as “baseline”. The budesonide effect was the difference between values after 6 months inhaled budesonide and placebo treatment. The prednisolone effect was the difference between values after three weeks prednisolone and at baseline. A clinically relevant “response” to corticosteroids was defined as an increase in FEV₁ of 12% and minimally 200 ml. Student’s t-test and non-parametric tests were used for comparisons, all inflammatory data except % neutrophils was not normally distributed. For normally distributed data the absolute differences were calculated, for non-normally distributed data ratios were calculated. For 0% eosinophils arbitrarily 0.1% was assigned when calculating ratios. Data obtained within 2 weeks prior to, or within 4 weeks after an exacerbation was not used in the analyses. When this was the case for data after 6 months’ treatment, the 3 months’ data were used instead (this was applied in 3 patients, all on placebo, the decision for exclusion was made prior to unblinding the data). The sample size of the study was determined for the primary parameter sputum % neutrophils. On the basis of an expected effect size of 15% and a standard deviation of 8% in a previously published study, 16 patients were calculated to be needed, using an alpha of 5% and a beta of 80%. Neutrophil and eosinophil counts were primarily expressed as percentage of non-squamous cell count and not as absolute cell count per g sputum for the better repeatability of the % values.

Additionally an analysis was performed in search for baseline data that predicted the clinical response in FEV₁. This was done by correlation analysis using baseline data (Pearson’s and Spearman’s correlation tests) and in a post hoc analysis, based on findings presented after commencing the present study, by dividing the study population in two groups by median values of FEV₁ as % predicted, reversibility in % predicted and sputum % eosinophils at baseline and by comparing the effects in current- and ex-smokers.

Results

Baseline and Run-in data

Nineteen patients (13 male) were enrolled in the inhaled treatment phase of the study (Table 1). Similar numbers had GOLD-stage 1, 2 or 3 and reversibility in FEV₁ was small (mean 4.8% predicted). Ten additional patients were enrolled but had to be withdrawn before randomisation, mainly due to one or more exacerbations in the corticosteroid-free run-in phase of the study. Two patients did not complete the inhaled treatment periods: one was withdrawn after an exacerbation and one withdrew consent. Baseline sputum neutrophil % count correlated significantly with FEV₁ % predicted (rho= -0.50, p=0.021). No such relation existed between FEV₁ and other sputum inflammatory parameters.
Median sputum % eosinophils increased during the corticosteroid-free run-in period (Figure 2).

**Inhaled budesonide effects on inflammation**

There were no statistically significant differences in sputum % neutrophil counts after inhaled treatments (Table 2). There were, however, differences in % eosinophils (Figure 2). After 3 months’ budesonide treatment, median sputum % eosinophils was 42% lower than after 3 months placebo (median 1.1% versus 1.9%, \( p=0.036 \)). From 3 to 6 months treatment, % eosinophils remained low under budesonide, but the % eosinophils

![Figure 2. Box-plots on sputum % eosinophils (logarithmic scale) at Entry in the study, at Baseline (B-L), after Prednisolone, after Wash-Out (W-O), after Placebo (Pla), after Budesonide (Bud) and at Exacerbations. Combined data after 3 and 6 months' budesonide and placebo treatment and all exacerbations where sputum data was collected.](image-url)
decreased under placebo and there remained a non-significant 31% difference (median 1.1% versus 1.6%, p=0.78). Eosinophil count per g sputum was 29% lower at 3 months (p=0.09) and 9% lower at 6 months (p=0.78). No significant differences were observed in median sputum levels of ECP, MPO, IL-8, α-2-macroglobulin and albumin. No relevant period effects or treatment–order effects were detected with respect to inflammatory parameters.

**Inhaled budesonide effects on lung function.**

After treatment with budesonide, compared to placebo, there were modest differences in lung function (Table 3). Of the 17 patients who completed the entire study, 3 patients (18%) were classified as “responder”, based on a clinically relevant difference in post-bronchodilator FEV₁. The mean difference for all patients in post-bronchodilator FEV₁ at 6 months was 75 ml (p=0.16) or 2.5% of predicted (p=0.091) in favour of budesonide treatment. There was no period effect (p=0.59) but a trend for a treatment–order effect (p=0.07) existed for the differences in FEV₁, fitting with an ongoing decline in lung function during placebo treatment. The difference in post-bronchodilator FEV₁ became 82 ml (p=0.12) or 2.7% predicted (p=0.063) after correction for treatment sequence. The difference in pre-bronchodilator FEV₁ after 6 months treatment was statistically significant: 140 ml (p=0.041) or 5.2% predicted (p=0.030). Other spirometry and body plethysmography parameters did not differ significantly (data not shown).

**Figure 3.** Relation between baseline FEV₁ (post-bronchodilator, % predicted) and budesonide-treatment induced changes in sputum % eosinophils (rho = −0.53, p=0.056), levels of MPO (rho = −0.46, p=0.076), IL-8 (rho = −0.58, p=0.025) and ECP (rho = −0.64, p=0.010), expressed as the ratio of the values after 6 months budesonide / after 6 months placebo treatment. A lower ratio represents a beneficial effect of budesonide.
Table 2. Effects of oral prednisolone and inhaled budesonide on inflammatory parameters in induced sputum.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>start prednisolone</th>
<th>3 weeks prednisolone</th>
<th>wash-out</th>
<th>p-value start vs 3 weeks</th>
<th>p-value 3 weeks vs wash-out</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-squamous TCC (10⁶/g)</td>
<td>0.96 (0.47-3.67)</td>
<td>2.19 (0.68-4.52)</td>
<td>1.36 (0.75-4.15)</td>
<td>0.41</td>
<td>0.51</td>
</tr>
<tr>
<td>Neutrophils (%)</td>
<td>74.5 (64.2-85.4)</td>
<td>82.6 (68.5-89.0)</td>
<td>74.4 (61.5-83.5)</td>
<td>0.26</td>
<td>0.22</td>
</tr>
<tr>
<td>Neutrophils (10⁶/g)</td>
<td>0.67 (0.25-2.72)</td>
<td>1.25 (0.46-4.03)</td>
<td>0.86 (0.46-3.14)</td>
<td>0.26</td>
<td>0.38</td>
</tr>
<tr>
<td>Eosinophils (%)</td>
<td>1.6 (0.8-3.4)</td>
<td>0.2 (0.0-0.7)</td>
<td>1.0 (0.3-2.4)</td>
<td>0.007</td>
<td>0.033</td>
</tr>
<tr>
<td>Eosinophils (10³/g)</td>
<td>15.2 (4.3-53.4)</td>
<td>15.2 (5.7-40.1)</td>
<td>14.6 (8.6-37.3)</td>
<td>0.21</td>
<td>0.12</td>
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<tr>
<td>MPO (μg/g)</td>
<td>7.2 (1.8-22.6)</td>
<td>10.2 (4.0-42.8)</td>
<td>7.0 (1.7-69.0)</td>
<td>0.21</td>
<td>0.12</td>
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<tr>
<td>IL-8 (ng/g)</td>
<td>4.6 (1.6-13.7)</td>
<td>3.1 (1.6-15.0)</td>
<td>4.7 (1.6-35.8)</td>
<td>0.21</td>
<td>0.12</td>
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<tr>
<td>ECP (ng/g)</td>
<td>287 (33-431)</td>
<td>140 (98-460)</td>
<td>220 (42-1921)</td>
<td>1.00</td>
<td>0.87</td>
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</table>

Values are shown as median (interquartile range) and per g sputum for the 17 patients who completed the study; wash-out: 3 weeks after completion of prednisolone treatment; p-values from Mann-Whitney tests; TCC: Total Cell Count; % neutrophils and eosinophils as % of non-squamous cells; MPO: Myeloperoxidase; IL-8: Interleukin-8; ECP: Eosinophil Cationic Protein

Table 3. Effects of oral prednisolone and inhaled budesonide on lung function

<table>
<thead>
<tr>
<th>Parameter</th>
<th>start prednisolone</th>
<th>3 weeks prednisolone</th>
<th>wash-out</th>
<th>p-value 3 months budesonide vs placebo</th>
<th>p-value 6 months budesonide vs placebo</th>
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<tbody>
<tr>
<td>FEV₁ (% pred, pre)</td>
<td>58.6±18.6</td>
<td>57.8±19.6</td>
<td>58.4±20.9</td>
<td></td>
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<tr>
<td>FEV₁ (% pred, post)</td>
<td>63.0±20.7</td>
<td>62.4±20.4</td>
<td>62.8±21.8</td>
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<td></td>
</tr>
<tr>
<td>FEV₁ (% pred, post)</td>
<td>3 months budesonide</td>
<td>6 months budesonide</td>
<td>3 months placebo</td>
<td></td>
<td></td>
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<tr>
<td>FEV₁ (% pred, pre)</td>
<td>57.3±18.9</td>
<td>57.6±21.7</td>
<td>55.7±18.1</td>
<td>52.4±15.7</td>
<td></td>
</tr>
<tr>
<td>FEV₁ (% pred, post)</td>
<td>61.7±20.0</td>
<td>62.1±22.4</td>
<td>60.9±19.4</td>
<td>59.6±18.0</td>
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</table>

Values are shown as mean ± SD for the 17 patients who completed the study, pre- and post bronchodilator; p-values from t-tests; wash-out: 3 weeks after completion of prednisolone treatment; pred: predicted normal.
Inhaled budesonide effects on other parameters

After 6 months’ inhaled budesonide treatment absolute and relative eosinophil counts in peripheral blood were significantly reduced, but at 3 months no significant differences were observed (data not shown). Total white blood cell count and % neutrophil count in blood were higher, absolute and % eosinophil count and % lymphocyte count were lower after 6 months budesonide treatment compared to placebo. No significant differences were observed in plasma levels of CRP (median 5.0 and 3.0 mg/l after 6 months’ treatment with placebo and budesonide respectively, p=0.39).

Relationship between lung function and inflammation

The difference in post-bronchodilator FEV₁ as % of predicted after 6 months treatment was significantly correlated with baseline FEV₁ as % of predicted (r=0.77, p<0.001). In addition, the changes in most inflammatory parameters in sputum at 6 months were also related to baseline FEV₁ (Figure 3). This was the case for changes in sputum ECP (rho= -0.643, p=0.010) in sputum IL-8 (rho= -0.58, p=0.025) and a tendency was observed for changes in sputum % eosinophils (rho= -0.53, p=0.056) and in sputum MPO (rho= -0.47, p=0.076). As a consequence, the change in FEV₁ was also significantly correlated with the changes in these inflammatory parameters (data not shown).

The magnitude of inflammation at baseline was not significantly related with the effects of budesonide on FEV₁ and inflammation (detailed data not shown, for baseline sputum % eosinophils versus effect on FEV₁: p >0.4). The study population was divided post hoc in two groups around the median for baseline FEV₁ (median 62.6 % predicted), reversibility in FEV₁ (median 2.22%
predicted), sputum % eosinophils (median 1.6%) and smoking habit. The group with the highest baseline FEV$_1$ showed the best response in FEV$_1$ to budesonide (+5.6 versus −0.9% predicted, p=0.014) as did the group with the largest degree of reversibility (+5.6% versus −0.2% predicted, p=0.034). A higher baseline sputum % eosinophils was not significantly related with a better response to budesonide (+4.2% versus +1.1% predicted, p=0.30). The effects of budesonide on inflammatory parameters and on FEV$_1$ did not differ significantly between current smokers and ex-smokers (all p>0.2).

**Prednisolone effects**

Prednisolone treatment did not decrease but rather slightly increased sputum % neutrophils (p=0.48, Table 2). Sputum % eosinophils decreased with 87%, from a median 1.6% to 0.2% (p=0.007, Figure 2). Sputum eosinophil count per g sputum was unchanged by prednisolone treatment (p=0.21) and other sputum parameters did not change significantly. Prednisolone markedly affected parameters in peripheral blood: total leukocyte count and % neutrophils increased significantly while % lymphocytes and % eosinophils decreased significantly as did CRP plasma levels (data not shown). After the wash-out period most values returned to those obtained prior to prednisolone treatment, though eosinophil counts did not completely return to baseline values in 3 weeks (Table 2). Prednisolone treatment did not influence lung function (Table 3) and none of the 19 patients could be classified as a “responder”.

**Relation between prednisolone and budesonide effects**

There were no significant correlations between the effects of prednisolone and budesonide on inflammatory parameters in blood and sputum (detailed data not shown), in particular not with respect to the effects on sputum % eosinophils (rho=0.19, p=0.52). The effect of prednisolone on FEV$_1$ did not correlate with that of budesonide (r= -0.30, p=0.24).

**Exacerbations**

Eight of the initial 29 patients experienced at least one exacerbation in the first four weeks of the run-in period and required medical intervention before they entered the actual prospective inhaled treatment phase or had to be withdrawn. These 8 patients had more severe disease than the 21 patients completing the run-in period without an exacerbation (FEV$_1$ 50.8 versus 68.1% predicted, p=0.037), they tended to have higher sputum eosinophil counts (1.6% versus 0.6%, p=0.20) and had significant higher blood % eosinophil counts (3.4% versus 2.0%, p=0.045). During the twelve months of blind inhaled treatment 18 exacerbations were observed, requiring antibiotic treatment, 9 of 18 were classified as severe, necessitating treatment with systemic corticosteroids: 3 during budesonide (3 patients) and 6 during placebo (4 patients). The proportion of exacerbations requiring systemic corticosteroid treatment was higher during placebo than during budesonide (6 of 8 versus 3 of 10, p<0.05). During the entire study, 8 sputum
samples were obtained within 2 weeks before or 4 weeks after an exacerbation, of which 4 during blind treatment. These data were excluded from the statistical comparisons: 3 samples after 6 months placebo (sputum % eosinophils 8.1%, 25.8% and 19.8%) and 1 sample after 3 months budesonide (sputum % eosinophils 1.8%). Median sputum % eosinophil count in all 8 samples around exacerbations was 5.5%, remarkably higher than values obtained during stable disease (Figure 2).

Discussion

The present study is the first study evaluating anti-inflammatory and clinical effects of long-term inhaled steroid treatment in COPD patients in a cross-over design. In the present group of patients with strictly defined smoking-related COPD and covering a broad spectrum of severity (GOLD 1 to 3), no effect was found of long-term inhaled budesonide on sputum neutrophilia. However, reductions were found on sputum eosinophils and on functional impairment (FEV₁). These anti-inflammatory effects and functional improvements were modest, went in parallel and appeared to be confined to a subgroup of patients with a milder disease in terms of irreversible functional impairment at enrolment. However, since the latter observation was not the primary aim of our study this finding must be interpreted with caution and need confirmation in larger studies. None of the inflammatory parameters was found to be predictive of the effects of long-term inhaled budesonide treatment. In line with two recent short-term studies, higher sputum eosinophilia at baseline tended to correlate to a larger clinical response to the inhaled glucocorticosteroid. In the present study this relation failed to reach statistical significance, likely due to low % eosinophil counts at enrolment or to selective withdrawal of patients with highest % eosinophil counts in the run-in phase where glucocorticosteroids were withdrawn. No evidence was found for a predictive value of assessing the short-term (clinical or anti-inflammatory) effects of oral prednisolone to the clinical or anti-inflammatory effects of long-term inhaled budesonide treatment.

With respect to the interpretation of our findings, especially the effects on airway eosinophils, it is highly relevant that patients were recruited according to strictly defined criteria for a diagnosis of COPD, though ranging in severity of airflow obstruction. As in previous studies, a correlation was observed between the severity of COPD in terms of FEV₁ and the % of neutrophils in sputum.

This study was primarily designed to investigate treatment effects on neutrophilic inflammation. However, we found no suppressive effects of either corticosteroid treatment on parameters of neutrophilic inflammation but an opposite trend. These observations are in contrast to some previous studies which described marked effects of corticosteroid
treatment on neutrophilic inflammation, but in line with other studies showing no such effects. The recent meta-analysis of a larger series of studies indicates that by increasing the data set by pooling the data of these potentially contradicting studies, inhaled corticosteroid treatment was shown to reduce both neutrophil and eosinophil counts in sputum.

During budesonide treatment, a tendency to a lower incidence of severe exacerbations was observed and a shift towards less severe exacerbations, in line with other, large-scale studies. In the few sputum samples obtained close to exacerbations, sputum % eosinophils was rather high. This provides further circumstantial evidence for a relation between exacerbations and eosinophils, hereby suggesting that budesonide may have influenced exacerbations by suppressing eosinophilic inflammation. The reported effects of long-term treatment with inhaled corticosteroids on decline in lung function, exacerbation frequency and mortality might therefore be attributed to an effect on eosinophilic inflammation rather than to suppression of neutrophilic inflammation.

The patients who had to be withdrawn from the study in the corticosteroid-free run-in period due to repeated exacerbations had higher eosinophil counts at enrolment and their exclusion may have led to a selective withdrawal of patients who were the most corticosteroid sensitive. In the remaining patients no immediate increase in exacerbations was observed when switching from active to placebo inhaled treatment. Probably in combination with the strict inclusion criteria, median sputum eosinophil count was rather low at baseline. In a number of other studies in COPD, sputum % eosinophils was much higher, leaving more room for a reduction by treatment.

The present study extends current knowledge that also documenting the effects on inflammation (besides those on lung function) of a test treatment with oral prednisolone has no value in selecting COPD patients for long-term inhaled treatment. This negative outcome is of clinical importance. No overall effect of oral prednisolone was observed and not a single patient who completed the prednisolone period could be classified as “responder”, using a predetermined difference in FEV₁ of 12% (minimally 200 ml), a proportion much lower than in previous studies, which varied between 10% and 50% and may be related to our strict selection criteria.

At first sight the absence of a functional response to prednisolone seems to be in contrast to the effect of prednisolone on sputum % eosinophils. However, the 6-fold decrease in median % eosinophils after prednisolone was accompanied by unchanged numbers of eosinophils per gram sputum. Obviously, a reduction in sputum eosinophils may require more than 3 weeks before affecting lung function.
Some (potential) limitations of this study need to be discussed. The sample size estimation was based upon an anticipated decrease in sputum % neutrophils, and therefore may have been underpowered for other parameters like sputum % eosinophils and FEV₁. It must be realized, that concentrations of inflammatory markers in induced sputum will represent an integral of probably a heterogeneous expression of these markers in various lung regions. This needs not necessarily be a disadvantage, but may contribute to variability. In our hands, within-patients variability of most inflammatory parameters is approximately 2- to 3-fold for most parameters, making the current sample size sufficient to detect the 42% decrease in % eosinophils at 3 months but not sufficient to detect the 31% difference at 6 months.

The present study used a randomised cross-over design for the inhaled treatment periods in order to minimise the variability. We recently reported between-patients variability to be twice as large as within-patients variability. Such a cross-over design carries the risk of carry-over effects, these effects were however not observed for the inflammatory parameters. A carry-over effect was present for FEV₁ and was attributed to an ongoing decline in lung function during placebo treatment. The recent meta-analysis indicated that 2 – 3 months treatment is sufficient for a suppression of airway inflammation in COPD. The long duration of the study had also a drawback, since due to the occurrence of exacerbations some data was missing after 6 months’ placebo treatment, that data had to be replaced with the 3 months’ data.

The present findings suggested that an “eosinophilic component” of the inflammatory process in the airways is of importance in COPD, even in carefully selected patients in whom on clinical grounds any “asthmatic component” has been ruled out. The differences between placebo and budesonide treatment in sputum % eosinophil counts tended to be correlated with the differences in FEV₁. Additionally, confirming other studies, % eosinophil count in sputum was rather high in the samples which could be obtained in the vicinity of exacerbations.

A remarkable finding was the discrepancy in the effect of budesonide compared to placebo on sputum eosinophils at 3 and 6 months. At 3 months the 42% difference was significant, but the 31% differences at 6 months not. This may be a chance finding in either direction, since the study was not primarily powered on sputum eosinophils. The effect of budesonide may also be temporal. However, the latter is unlikely since the difference between budesonide and placebo from 3 to 6 months diminished due to a decrease in eosinophils under placebo, not due to an increase under budesonide. More likely, the exclusion of sputum data obtained in the vicinity of exacerbations favoured the placebo treatment since the excluded samples obtained under placebo treatment had high % eosinophil counts.
The present findings do not provide easy to apply tools for a more individualised selection of COPD patients for inhaled corticosteroid therapy based on the assessment of their inflammatory profile in a single measurement during stable disease or based on a prednisolone test treatment. Rather, they underscore the heterogeneity of COPD with respect to the characteristics of airway inflammation during stable disease and exacerbations and the clinical response to corticosteroid therapy. The observed anti-inflammatory effects and functional improvements by long-term treatment with budesonide may be confined to those with a specific COPD in terms of higher baseline FEV$_1$ as % of predicted, airflow reversibility and sputum eosinophil counts.

At present, inhaled corticosteroids are indicated in COPD patients at the more severe end of the disease spectrum (FEV$_1$ < 50%), in whom they have been shown to prevent up to 30 % of severe exacerbations.$^{2,3}$ We hypothesize that at least part of this effect of inhaled corticosteroids on exacerbations is based upon the suppression of a supplementary eosinophilic inflammation during or immediately prior to exacerbations of COPD. It is obvious that this hypothesis needs confirmation from a study specifically designed to answer such a research question.

Acknowledgements

We gratefully acknowledge P. Teiwes, who performed most of the lung function tests and the collection of induced sputum. The study was supported by a research grant from AstraZeneca, The Netherlands under study number BN-00P-0087. Parts of the present data were presented at the European Respiratory Society congresses in Vienna, September 2003, and Copenhagen, September 2005.
Effects of budesonide on inflammation in COPD

References


