Topical Review

Are anti-oxidant and anti-inflammatory treatments effective in different subgroups of COPD?
A hypothesis

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The treatment of chronic obstructive pulmonary disease (COPD) with inhaled corticosteroids or anti-oxidants is still under debate and the identification of sub-groups of COPD patients who may benefit from either anti-inflammatory or anti-oxidant treatment is needed.

We re-analysed data from an earlier study of inhaled beclomethasone therapy in COPD (n=28) and asthma (n=28) patients in order to determine patient characteristics that predict a favourable inhaled steroid treatment effect.

A higher bronchodilatory response, a faster decline of FEV₁ prior to the treatment period and a lower Tiffeneau index were significantly related to more beneficial treatment effects. Increased smoking tended to be related to less steroid treatment benefits, though it was not statistically significant. In this paper these findings are presented in light of the available literature on anti-inflammatory and anti-oxidant COPD treatment.

On this basis the hypothesis is presented that anti-oxidant treatment might be relatively more effective among those COPD patients who respond less well to inhaled steroids (low reversibility and heavy smoking).

Introduction

We discuss here possible agents that may alter the decline of lung function in chronic obstructive pulmonary disease (COPD) patients. At the recently held annual congress of the European Respiratory Society, the results of a large multi-centre trial into COPD (the EUROSCOP study were presented (1). Within a large group of heavy smokers with pulmonary obstruction and a very low reversibility, a 3-year daily dosage of 800 µg budesonide was compared to placebo and appeared to be only minorly beneficial to the course of the post-bronchodilator FEV₁. Furthermore, at the congress the present state of several other, large, long-term studies on the role of inhalation corticosteroids (ICS) in COPD were presented (ISOLDE, Copenhagen City Lung Study, Lung Health Study II). These studies differ from each other in severity of the COPD subjects and pharmacological agents used. In addition to these ICS trials a recently initiated large trial among COPD patients was presented in which the efficacy of the anti-oxidant N-acetylcystein will be studied (BRONCUS). All these trials aim to study the effect of these drugs on the decline of the postbronchodilator FEV₁.

It is likely that inflammatory mechanisms as well as oxidative mechanisms play an important role in the development and progression of COPD (2,3). Morphological changes in chronic bronchitis are characterized by mucous gland hypertrophy and hyperplasia, goblet cell metaplasia, smooth muscle hypertrophy and loss of ciliary function, associated with mononuclear inflammatory cell infiltration (2,4). Mucus hypersecretion and reduction in mucociliary clearance may cause mucus retention in the airways facilitating viral or bacterial superinfection (5). The presence of bacteria or viruses is thought to cause an alteration of host defences with accumulation of neutrophils, macrophages and T lymphocytes in the bronchial mucosa (6). Moreover, the process may become self-perpetuating with the release of cytokines and substances with proteolytic action. Activated neutrophils, which are increased in sputum during acute exacerbations, can cause lung tissue damage.
DIFFERENT TREATMENT IN COPD SUB-GROUPS

Table 1. Relationship between clinical characteristics and change in FEV, during 2-year 800 μg beclomethasone treatment daily as assessed by ANCOVA in 28 patients with asthma and 28 patients with COPD [based on a re-analysis of an earlier published study (28)]. The estimate of FEV, is given in 10^-3 l (SEM in parentheses.) Two-tailed P-values <0.05 were considered statistically significant.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>P-value</th>
<th>Estimate</th>
<th>P-value</th>
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<tbody>
<tr>
<td>COPD</td>
<td></td>
<td></td>
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<tr>
<td>Pack-years</td>
<td>-4.6 (5.1)</td>
<td>0.38</td>
<td>-3.2 (5.0)</td>
<td>0.54</td>
</tr>
<tr>
<td>Smoking (±)</td>
<td>-319 (176)</td>
<td>0.086</td>
<td>-136 (142)</td>
<td>0.35</td>
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<tr>
<td>Allergy (±)</td>
<td>-81 (430)</td>
<td>0.85</td>
<td>220 (131)</td>
<td>0.11</td>
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<tr>
<td>FEV,VC (%)</td>
<td>15.6 (6.0)</td>
<td>0.018</td>
<td>-6.6 (5.2)</td>
<td>0.21</td>
</tr>
<tr>
<td>Slope-FEV, (10^-3 1yr^-1)</td>
<td>1.7 (0.3)</td>
<td>0.0001</td>
<td>1.8 (0.5)</td>
<td>0.001</td>
</tr>
<tr>
<td>BDR-FEV, (l)</td>
<td>0.95 (0.11)</td>
<td>0.001</td>
<td>0.76 (0.71)</td>
<td>0.002</td>
</tr>
<tr>
<td>2logPC20</td>
<td>-3.9 (17.7)</td>
<td>0.83</td>
<td>-45.6 (20.9)</td>
<td>0.066</td>
</tr>
<tr>
<td>DI-PEFR (%)</td>
<td>6.0 (12.9)</td>
<td>0.65</td>
<td>13.11 (6.4)</td>
<td>0.052</td>
</tr>
<tr>
<td>CV-PEFR (%)</td>
<td>27.7 (29.4)</td>
<td>0.36</td>
<td>11.7 (15.1)</td>
<td>0.45</td>
</tr>
<tr>
<td>Asthma</td>
<td></td>
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Slope-FEV, Annual decline in FEV, in 2 years before steroid treatment; BDR-FEV, bronchodilating response in FEV, 60 min after ipratropium 80 μg and salbutamol 400 μg; CV-PEFR, week-to-week coefficient of variation of the PEFR; DI-PEFR, diurnal PEFR index (absolute difference between evening and morning value divided by the highest value; FEV, forced expiratory volume in 1 s; PC20, provoking concentration of histamine producing a 20% fall in FEV; SEM, standard error of the mean.

variables assessed before the start of steroid treatment were related to the changes in FEV, during the 2-year steroid treatment period by means of analysis of covariance (ANCOVA). By this procedure it can be estimated which variable predicts best the decline in FEV, during steroid treatment, in other words, which features determine whether patients benefit most from steroid treatment. The estimates in the slope (β) and P-values were calculated and are presented in Table 1. The larger the estimate of the variable in relation to the SEM (given between brackets) the more significantly the variable concerned contributes to the FEV, decline. To compare the effects in COPD with asthma, the same analysis was done for asthma. Table 1 shows that in patients with COPD, the improvement in FEV, during steroid treatment was larger in patients with more airway obstruction (as assessed by the FEV,VC), a higher reversibility of this obstruction and a larger decline in FEV, before steroid therapy. A non-significant influence of current smoking was found (P=0.086) in COPD: current smokers seemed to respond worse on inhaled steroids. These observed effects in COPD were only apparent during the first 6 months of treatment with the inhaled steroid. In asthma we found, besides the larger decline in FEV, before steroid therapy and the higher reversibility, tendencies towards a better response in patients with a higher diurnal peak-flow rate index and a more severe degree of bronchial hyperresponsiveness (P=0.052 and P=0.066, respectively).

In discussing the possible predictors of a long-term response on ICS, it should be kept in mind that the latter studies (28,29), apart from the EUROSCOP study, were not primarily set up for this purpose. Our study concerned a selective group of patients with COPD: all patients were selected on the criterion that they had a decline in lung function of more than 80 ml yr^-1, which made them less representative for all patients with COPD (28). As the variability in lung function is considerable, most studies lack the power for adequate sub-group analysis, which withholds their results from generalization into other populations. Therefore the results of the clinical trials of ICS in COPD (Copenhagen City Lung Study (CCLS), ISOLDE study, Lung Health Study II) will be of great importance in concluding whether definite sub-groups of COPD may benefit specifically from ICS.

Treatment of COPD with N-acetylcysteine (NAC)

Another (much less investigated) possibility in the treatment of COPD is long-term use of N-acetylcysteine (NAC). NAC is the N-acetyl derivative of the amino acid cysteine, which is used as a mucolytic agent and as a precursor of glutathione in the treatment of paracetamol overdosing. Several controlled clinical trials in patients with chronic bronchitis have shown that a 6-month treatment with NAC (400–600 mg day^-1) improved respiratory symptoms, and reduced the rate and duration of exacerbations as well as the number of sick-days (32–34).

Originally, the therapeutic efficacy of NAC was ascribed to its ability to reduce mucus viscosity and to improve mucociliary clearance (35,36). Subsequent studies have shown that NAC is an anti-oxidant agent which may protect lung tissue against oxidant-induced damage and can inhibit the epithelial thickening and secretory cell hyperplasia induced by cigarette smoke in rats (37,38).
through the release of proteases (elastase), enzymes (myeloperoxidase) and generation of oxygen radicals (7). Consequently, an infiltration of inflammatory cells causes further epithelial damage and wall thickening of small airways (2). Small airways disease is presently thought to be strongly related to the development of emphysema (8,9).

Increased numbers of reactive oxygen species (ROS) are present in the lungs of patients with COPD, as a direct result of inhalation (cigarette smoke) or increased production by activated inflammatory cells and activation of the xanthine oxidase pathway. These oxidants may inactivate $\alpha_1$-AT, one of the main inhibitors of elastase (10), thus contributing to parenchymal damage and loss of lung function. Maier et al. showed that bronchoalveolar lavage fluid (BALF) of smokers with chronic bronchitis contained more oxidized methionine residues of $\alpha_1$-proteinase inhibitor than healthy subjects (11). Another method to show increased numbers of ROS in the lungs is measurement of the concentration of hydrogen peroxide ($H_2O_2$) in exhaled breath. Recently, it was shown that stable COPD patients exhaled significantly more $H_2O_2$ than healthy controls (12). In addition, patients with unstable COPD, during exacerbations, had a higher concentration of $H_2O_2$ in their exhaled air, compared to those with stable COPD, indicating increased oxidative stress (12). Furthermore, a reduction in anti-oxidative capacity in plasma was found during acute exacerbations of COPD (13).

Both the inflammatory and the oxidative mechanisms may provide additional treatment possibilities. A primary goal in the treatment of COPD is to reverse or attenuate the accelerated loss of lung function in the long term. For now the treatment spectrum includes avoidance of initiating and aggravating triggers such as tobacco smoke and specific work-related irritants. Other non-pharmacological treatment modalities include nutrition, immunization against influenza, supplemental oxygen, breathing exercises and pulmonary rehabilitation. Optimal bronchodilatation should be sought using inhaled anticholinergics and/or $\beta_2$-sympathomimetic drugs. While most COPD patients still experience accelerated loss of ventilatory capacity, the identification of sub-groups of COPD patients that may benefit from additional anti-inflammatory or anti-oxidant treatment becomes pressing. In this paper we intend to contribute to this discussion.

**Treatment of COPD with inhaled corticosteroids (ICS)**

As ICS are very efficacious in asthma, many patients with COPD are also treated with them. The type of inflammation in COPD, however, differs from asthma and it has become apparent that the long-term efficacy of ICS in COPD is less obvious compared to asthma (14–16).

Most short-term studies in COPD showed that ICS have some (small) beneficial effects on lung function (17–23), but others did not show an improvement (24–26). None of these studies showed any effect on bronchial hyperresponsiveness and had only a small effect on symptoms (24,25).

In general, long-term studies showed a similar tendency (27–29): small improvement in lung function, no change in bronchial hyperresponsiveness, decrease of symptoms to a small extent (27,28) and a small reduction in the number of exacerbations (28,29).

The results of the EUROSCOP study, the largest long-term study, concur with this (1). Budesonide inhaled for 3 years at $800\mu g$ day$^{-1}$, was shown to have only a small beneficial effect on lung function among heavy smokers with mild COPD and a low reversibility (ERS, Berlin and Geneva). However, the improvement of $FEV_1$ was mainly due to the first 3–6 months of treatment. After this initial benefit, the $FEV_1$ level paralleled the same linear decline as in the placebo group. This pattern an initial benefit of ICS treatment on the $FEV_1$ level occurring in the first 3–6 months, followed by a parallel decline to the placebo group was observed earlier in COPD and suggests that a major part of the chronic airway obstruction in COPD cannot be influenced by long-term ICS treatment (28). In this regard, identification of clinical characteristics which may predict a favourable response of COPD patients to ICS with regard to the long-term course of $FEV_1$, seems sensible and (urgently) needed (30,31).

In a mixed group of asthma and COPD patients ($n=91$) treated with beclomethasone $800\mu g$ daily for 30 months, subjects who did not smoke, had allergy or were less than 40 years old benefited more from ICS (i.e. improvement in lung function) than those who smoked, did not have allergy and were over 40 years (29). A further analysis of this study showed that bronchodilator response, bronchial hyperresponsiveness, total IgE and smoking habits were all independent predictors of the treatment response to ICS (30). A problem in this study was that no distinction was made between asthma and COPD and the inclusion criteria (increased hyperresponsiveness and reversibility of obstruction) tended to select more asthmatics than patients with COPD. So on the basis of this study no firm conclusion can be drawn about predictors of a long-term response on inhaled steroids in COPD.

The EUROSCOP study identified less heavy smoking history (less pack-years) as a determinant of a positive response to ICS. Furthermore, it was observed that in addition to the initial effect in the first 3–6 months, the benefits of ICS for less heavy smokers increased slowly during the remaining years of the study. A non-significant trend was observed for more treatment effect of ICS among subjects with more reversibility. However, as the subjects of this study were selected on the basis of a very low reversibility, this design may not allow a definite evaluation of the influence of reversibility. Surprisingly paediatric status and age were not correlated with the response to ICS in this population.

We have analysed the data of our study (28) in order to investigate which sub-groups of patients with COPD responded most to inhaled corticosteroids in this study. This study concerned a 4-year study in which 28 patients with asthma and 28 with COPD used no inhaled steroids for 2 years followed by 2 years of using $800\mu g$ beclomethasone dipropionate daily. Our hypothesis was that COPD patients with more asthmatic features would benefit most from treatment with inhaled steroids. Therefore, the
Moreover, NAC penetrates into cells, where it is deacetylated to l-cysteine, thus supporting the biosynthesis of glutathione, which is one of the most important antioxidant systems in the cell. Indeed, the maintenance of intracellular glutathione stores plays a key role in the cell protection (39). In an in vitro study NAC has been shown to inhibit neutrophil and monocyte chemotaxis and oxidative burst responses (40). In smokers, NAC (600 mg day\(^{-1}\) orally) decreases lysozyme and lactoferrin concentrations and reduces the activation and number of neutrophils and alveolar macrophages, recovered from BAL fluid (41–43). NAC has also been found to protect \(\alpha_1\)-AT against oxidative inactivation (10). The decrease in the incidence of exacerbations may be explained by a decrease in bacterial colonization by Streptococcus pneumoniae and Haemophilus influenzae in the airways of chronic bronchitis during treatment with NAC (44).

An open study in patients with mild-to-moderate COPD suggested that NAC could reduce the yearly decline in lung function (45). This effect was most pronounced in patients who were older than 50 years of age. A direct link between these clinical effects (i.e., reduction in the number of exacerbations and reduction in the decline of lung function) and its anti-oxidative capacity as mechanism of action, however, has not been established thus far. Long-term prospective studies investigating this are just beginning.

**Hypothesis**

These observations have brought us to the hypothesis that the anti-oxidant effect of NAC might be most efficacious in COPD patients who are heavy smokers with a largely irreversible airflow obstruction. In other words, NAC might be most efficacious in those subjects who are less responsive (or even resistant) to ICS (see Fig. 1). This hypothesis could be tested in a long-term placebo controlled randomized trial with ICS and NAC in COPD patients with a wide variety of possible determinants (such as smoking behaviour, reversibility of obstruction, age, etc). The Dutch Health Insurance Council and the Dutch Asthma Foundation have recently decided to support such a study (the Co-opt study). If this hypothesis is true it will have important consequences for the daily treatment of COPD. At the moment no serious alternatives are available for steroid therapy, although we know that the effects of these drugs in COPD are very limited.

**References**


10. Aruoma OI, Halliwell B, Hoey BM, Butler J. The antioxidant action of N-acetylcysteine: its reaction with


