EDITORIAL

Do patients with COPD benefit from treatment with inhaled corticosteroids?

C.P. van Schayck*, P.M. van Grunsven, P.N.R. Dekhuijzen

In the past few years, treatment with inhaled corticosteroids has become increasingly important in asthma [1, 2]. It appears that inflammation of the airway wall is a major pathophysiological mechanism underlying asthma [3], and perhaps also chronic obstructive pulmonary disease (COPD) [4]. Some long-term studies in asthmatic patients over 1 and 2 yrs have shown that maintenance treatment with inhaled corticosteroids is beneficial [5–7]. In contrast to asthma, the efficacy and therefore the precise role of inhaled corticosteroids is less clear in the treatment of patients with COPD [8, 9]. Corticosteroids are generally given in COPD, in order to treat exacerbations, for a relatively short period of time. The efficacy of long-term treatment with inhaled steroids is not yet established. Whilst in asthma the response is rapid, there are indications that (some) patients with COPD may only respond adequately to (oral) corticosteroids after 6 months to 2 yrs of therapy [10]. We have, therefore, investigated the literature over the past 15 yrs on short-term as well as long-term response to inhaled steroids in COPD. This was done by means of a Medline Search (MeSH headings and/or free text words: anti-inflammatory-agents-steroidal; chronic airflow obstruction; COPD-chronic obstructive pulmonary disease). Only randomized controlled studies (English-written) with inhaled steroids were included. Special attention was paid to possible predictors of a long-term response to inhaled steroids in COPD.

Effects of inhaled steroids in COPD

Of the 103 studies found in Medline, only 14 matched the inclusion criteria. Most of these studies were short-term studies, ranging from 2 weeks to 3 months [11–20]. Only a few long-term prospective studies with inhaled corticosteroids in COPD were available, ranging 12–30 months [21–24], of which one study [22] was the (24 month) follow-up of a 12 month study [21]. The other long-term study [23] did not make a distinction between asthma and COPD but studied *post-hoc* a group with a symptom-based diagnosis of COPD. There was one other study published in abstract form only, of long-term controlled use of inhaled steroids in COPD [25].

Table 1 presents an overview of the design and results of these studies. Most short-term studies show that inhaled steroids have beneficial effects on lung function (forced expiratory volume in one second (FEV₁), forced vital

capacity (FVC) and peak expiratory flow rate (PEFR)) when given in dosages of 1,500–3,000 µg beclomethasone daily for 2–6 weeks [11–17]. When compared with oral steroids, the effects of inhaled steroids on lung function were less pronounced [11–15]. Lower dosages of budesonide (800–1,600 µg) for 8 weeks to 3 months did not result in a significant improvement in lung function [18–20]. None of these studies showed any effect on bronchial hyperresponsiveness as assessed by the provocative concentration of agonist producing a 20% fall in FEV₁ (PC₂₀), although high doses of beclomethasone may have some effect on the inflammation assessed by means of bronchoalveolar lavage (BAL) [17]. Two studies showed small effects on one specific symptom (dyspnoea and cough) but not on symptom scores in general [18, 19].

Long-term studies with 800–1,600 µg beclomethasone or budesonide for 12–30 months [21–25] generally showed the same tendency: small improvements in lung function (FEV₁, FVC and PEFR), but no change in bronchial hyperresponsiveness (PC₂₀). During inhaled steroid usage, symptoms decreased to a small extent [22, 24], and there was a small reduction in the number of exacerbations [22, 23] or the days of oral steroid use during exacerbations [25]. As could be expected, the treatment benefits of inhaled corticosteroids were much more pronounced in patients with asthma than in those with COPD [21–23]. In asthma, inhaled steroids not only markedly improved the level of lung function and bronchial hyperresponsiveness, but also the yearly decline in lung function (the progression of the disease) to a far greater extent than in COPD. For instance, in one study [22], the average increase in FEV₁ during steroid therapy in COPD was 0.098 L, which was only 43% of the 0.228 L increase in asthma. In the same study, the PC₂₀ decreased by 3.2 doubling doses in COPD, whereas in patients with asthma an increase of 2.1 doubling doses was found during the same period ($p < 0.05$).

Predictors of a long-term response to inhaled steroids in COPD

So far, there has only been one study investigating the predictors of a long-term response to inhaled steroids [23]. Within a group of 91 patients, treated with beclomethasone 800 µg daily for 30 months, it was shown that subjects who did not smoke, who had allergies, or who were less than 40 yrs of age benefited more from their treatment (improvement in lung function) than did those who smoked, did not have allergies, or were over 40 yrs of age. A further analysis of this study showed that the

*Correspondence: C.P. van Schayck, Dept of General Practice, Nijmegen University, P.O. Box 9101, 6500 HB Nijmegen, The Netherlands.

Table 1. – Summary of studies published so far concerning the effect of inhaled steroids in COPD

[Ref.]	Pts n	Therapy $\mu\text{g}\cdot\text{day}^{-1}$	Design	Drop-outs	Results
Short-term studies					
[11]	12	Beclomethasone 1,600, 2 weeks	Double-blind/"cross-over" comparison	-	FEV ₁ ↑, but less than with prednisone
[12]	83	Beclomethasone 1,500, 2 weeks	Double-blind/"cross-over" comparison	-	FEV ₁ , FVC and PEFR ↑, but less than with prednisolone
[13, 14]	127	Beclomethasone 1,500, 2 weeks	Double-blind/"cross-over" comparison	-	FEV ₁ , FVC and PEFR ↑, but less than with prednisolone
[15]	107	Beclomethasone 1,500, 2 weeks	Double-blind/"cross-over" comparison	-	FEV ₁ , FVC and PEFR ↑, but less effective than prednisone in emphysema
[16]	105	Beclomethasone 1,500 vs 3,000, 3 weeks	Double-blind/"parallel" comparison	-	FEV ₁ , FVC and PEFR ↑, no difference between 1,500 versus 3,000 μg ; PC ₂₀ no change; QOL ↑
[17]	30	Beclomethasone 2,000, 6 weeks	Double-blind/"parallel" comparison	-	FEV ₁ , FVC ↑; inflammation (BAL) ↓
[18]	24	Budesonide 1,600, 8 weeks	Double-blind/"parallel" comparison	3	FEV ₁ , FVC, PEFR, rescue medication and PC ₂₀ no change; symptoms (only dyspnoea) ↓
[19]	25	Budesonide 800, 12 weeks	Double-blind/"parallel" comparison	7	FEV ₁ , FVC and PC ₂₀ no change; symptoms (only cough) ↓
[20]	14	Budesonide 1,200, 3 months	Double-blind/"cross-over" comparison	-	FEV ₁ , FVC and PC ₂₀ no change
Long-term studies					
[21, 22]	28	Beclomethasone 800, 12/24 months	Single-blind/"within-patient" comparison	6	FEV ₁ , FVC and PEFR ↑; PC ₂₀ no change; symptoms, exacerbations (only during 24 months [22]) and diurnal variation PEFR ↓
[23]	39/274 [†]	Beclomethasone 800, 30 months	Double-blind/"parallel" comparison	12 in steroid group versus 44 in control group	FEV ₁ ↑; exacerbations ↓; PC ₂₀ no change [‡]
[24]	58	Budesonide 1,600, 24 months	Double-blind/"parallel" comparison	2/40 in steroid versus 5/18 in control group	Symptoms decreased; FEV ₁ and exacerbations a nonsignificant improvement
[25] [#]	194	Beclomethasone 1,500, 24 months	Double-blind/"parallel" comparison	24	FEV ₁ and PEFR ↑; less oral steroid days (during exacerbations)

[†]: 39 subjects out of 274 had a symptom-based diagnosis of COPD, drop-outs are given for the total group of 274 patients, results only for the 39 COPD patients; [#]: published only in abstract form. COPD: chronic obstructive pulmonary disease; [Ref.]: reference number; Pts: patients; FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; PEFR: peak expiratory flow rate; PC₂₀: provocative dose of agonist producing a 20% fall in FEV₁; QOL: quality of life; BAL: bronchoalveolar lavage; ↑: increased; ↓: decreased.

bronchodilator response, PC₂₀, total immunoglobulin E (IgE) and smoking habits were all independent predictors of the treatment response to inhaled steroids [26]. As already mentioned, a problem in this study was that no distinction was made between asthma and COPD, and the inclusion criteria of this study (increased hyperresponsiveness and reversibility of obstruction) tended to select more asthmatics than patients with COPD. Therefore, on the basis of this study, no firm conclusion can be drawn about predictors of a long-term response to inhaled steroids in COPD. We have, therefore, analysed the data from our study [22], in order to investigate which subgroups of patients with COPD respond most to inhaled corticosteroids [27]. Our hypothesis was that COPD patients with more asthmatic features would benefit most from long-term treatment with inhaled steroids. The improvement in FEV₁ during steroid treatment appeared to be greater in patients with more airway obstruction (as assessed by the FEV₁/vital capacity (VC)), a higher reversibility of this obstruction, and a larger decline in FEV₁ before steroid therapy. Current smokers and smokers with more pack-years showed a worse response to inhaled steroids.

Clinical consequences

In discussing possible predictors of a long-term response to inhaled steroids, it has to be kept in mind that the studies referred to [22, 23] were not set up for this purpose. For instance, in our study [22], which concerned a selective group of patients with COPD, all patients were selected on the basis that they had a decline in lung function of more than 80 mL·yr⁻¹, which made them less representative of all patients with COPD or asthma. With this limitation in mind, there are indications that in COPD, the bronchodilating response at the start of steroid treatment and the annual decline FEV₁ in the preceding period appear to be predictors of the response to the inhaled steroid. Airways that respond only slightly to bronchodilators after a significant decline in lung function may have some degree of damage, such as loss of lung elastic recoil, hypertrophy of airway smooth muscle and thickening of the basement membrane, which may, in some instances, not be reversed either by bronchodilators or by corticosteroids [28, 29]. It is not only in long-term studies that the acute bronchodilating response has been shown to be an important predictor of

the long-term response to inhaled steroids. In short-term studies with systemic corticosteroids in patients with COPD, a significant relationship was also found between the bronchodilating response and the response to steroids [30–32].

It is possible that patients with the largest increase in airway obstruction during a period when no anti-inflammatory treatment is given, will demonstrate the largest improvements in FEV₁ during treatment with the inflammation-reversing corticosteroids. Therefore, in patients with COPD, a large annual decline in FEV₁ in the absence of anti-inflammatory treatment is possibly a useful indication for additional treatment with inhaled corticosteroids. It is possible that in these patients smoking plays a less dominant role in the pathogenesis (or progression) of COPD. Current smoking and having a more severe smoking history appeared to be related to the response to inhaled steroids in patients with COPD [22, 23]. This points to the relevance of the amount and duration of smoking to the long-term response to inhaled corticosteroids. More pack-years may be accompanied by more (irreversible) damage to the airways and a lower sensitivity to corticosteroids in COPD. A steroid response in COPD seems to be lowest in subjects with a slow, irreversible deterioration in lung function, probably caused by long and heavy smoking. In patients with a rapidly progressive form of COPD, we hypothesize that treatment with inhaled corticosteroids is probably indicated because of the increased risk of early morbidity and mortality in patients with a low lung function level and a high annual decline in lung function [33, 34]. Large prospective studies in a wide range of patients with COPD are clearly warranted to test this hypothesis. Data from large international studies, such as the Euroscop study, will become available in the near future [35].

It has not yet been proved that COPD patients with typical asthmatic features have a better response to inhaled corticosteroids. Apart from the reversibility, other features of asthma such as a high bronchial hyperresponsiveness and a high diurnal variation of the peak flow did not appear to be the most important determinants of the response to inhaled corticosteroids in COPD [27]. Asthmatic features were predictors of the steroid response in the study of KERSTJENS *et al.* [26]. However, this might have been caused by the asthmatic subjects in their mixed study group [23]. Both bronchial hyperresponsiveness (*i.e.* PC₂₀ ≤ 8 mg·mL⁻¹) and high diurnal variations of the peak flow (*i.e.* >15%) are important features of asthma [3, 36], which are very much related because they both express bronchial lability of the airways of asthmatics [36]. The degree of nonspecific bronchial responsiveness is closely related to the severity of inflammation in asthma [3]. Therefore, it seems logical that asthmatic subjects with severe bronchial hyperresponsiveness demonstrate the largest responses to inhaled corticosteroids.

It is possible that bronchial hyperresponsiveness in asthma is not the same as in COPD. JAMES *et al.* [37] found no relationship between PC₂₀ and response to corticosteroids in patients with COPD. It is possible that bronchial hyperresponsiveness in COPD does not signify inflammation as it does in asthma, but is rather an expression of the degree of existing airway obstruction [38,

39]. In none of the COPD studies could any influence of inhaled steroids on bronchial hyperresponsiveness (assessed by means of PC₂₀) be observed [11–25]; whilst in all of the asthma studies, a significant reduction of bronchial hyperresponsiveness was shown [5–7, 21–23]. It seems probable that the inflammation in COPD is less responsive to inhaled corticosteroids than it is in asthma. This might be caused by the high steroid sensitivity of lymphocytes and eosinophils, which are found in relatively high numbers in asthma but to a lesser extent in COPD in BAL studies [40].

In conclusion, use of inhaled steroids in chronic obstructive pulmonary disease seems to have some (in part dose-dependent) beneficial effects on lung function but not on bronchial hyperresponsiveness. Inhaled corticosteroids in chronic obstructive pulmonary disease may have some small effects on bronchial symptoms and exacerbations. There are indications that more reversibility of the airway obstruction and less smoking might be related to a better long-term response to inhaled steroids in chronic obstructive pulmonary disease. However, before translating this to clinical practice, more data are urgently needed to support these observations. Long-term data with inhaled steroids in chronic obstructive pulmonary disease will soon become available.

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