Inhaled steroids in chronic obstructive pulmonary disease

This issue of the Canadian Respiratory Journal contains an interesting paper by Gauvreau et al (pages 26 to 32) concerning inhaled steroids and allergic bronchoprovocation in patients with asthma. They looked at data from previous studies that showed that steroids attenuate both early and late airway responses to allergens, and that this was associated with a reduction in sputum eosinophilia. The new finding is that the presence of neutrophils in the sputum blunted the increase in sputum eosinophils seen with allergen challenge. Gauvreau et al postulated that neutrophils and, presumably, neutrophilic inflammation may reduce the response to steroids in asthma. This is a little tricky, because the level of sputum neutrophils did not influence the degree of bronchoconstriction produced by allergen inhalation. Nevertheless, it seems reasonable to suppose that neutrophilic inflammation is less sensitive to steroids than that due, in large part, to eosinophils, and the hypothesis gives me the opportunity to consider the effects of inhaled steroids in chronic obstructive pulmonary disease (COPD), a disease characterized by neutrophilic inflammation.

The effects of steroids in COPD have been controversial for a long time. Current guidelines (1) reflect ambiguity, recommending trials of high dose systemic steroids with subsequent steroid therapy in 'responders', an often poorly defined group. I believe that the situation has been clarified, to a large extent, over the past three to five years, with the publication of several large clinical trials of inhaled steroids in COPD, and I will share my view of the situation.

One thing seems indisputable. Inhaled steroids have no effect on the long term progression of COPD if one defines the progression in terms of rate of decline of forced expiratory volume in 1 s (FEV₁), which I would argue is the best approximation available. This has been shown in smokers with subclinical disease (2), in smokers with mild disease (3), in people with mild to moderate disease (4) and in patients with moderate to severe disease (5,6). Inhaled steroids are not disease modifiers in COPD; they apparently do not influence the inflammation and obstruction of small airways or the development of emphysema. Smoking cessation remains the only therapeutic manoeuvre that has been shown to change the long term outlook in COPD.

On the other hand, there is fairly good evidence that inhaled steroids are associated with a relatively small, one-time increase in the FEV₁ in patients with stable COPD. This appears to amount to 50 to 200 mL and is evident within weeks of commencing therapy. Changes of this type were seen in two of the major clinical trials (3,5) and have been observed in other studies of patients with established disease (7). Because the change is small, one needs to study a large group of patients to observe it, and its clinical significance is also probably small. The mechanism of this change is unknown. The change is of the same order of magnitude as the increase in FEV₁ observed immediately after stopping smoking and may be related to a decrease in endobronchial inflammation. It may well be that the salutary effect of systemic steroids in exacerbations of COPD are due to this effect; the differences between steroid and control groups in terms of lung function in exacerbation studies is of the order of 50 to 200 mL (8). On the other hand, it is possible that the processes underlying exacerbations increase steroid responsiveness in COPD. Certainly, some COPD exacerbations clinically resemble asthma attacks, and may be attended by eosinophilic inflammation.

Finally, there is evidence that inhaled steroids reduce the frequency and/or the severity of exacerbations. If this is true, it is important, because exacerbations cause most of the hospitalizations associated with COPD. I would argue that the effect of inhaled steroids on exacerbations merits further study for several reasons. In the first place, exacerbations are difficult to measure, both in terms of quality and quantity, and few of the studies that are available examined them prospectively using strict definitions. Second, there are studies that failed to show an influence on exacerbation frequency or severity; some are published (3,6) and some are not, reflecting publication bias. Nevertheless, the Inhaled Steroids in Obstructive Lung Disease in Europe (ISOLDE)
study (5) showed a substantial decrease in exacerbation number and an associated improvement in quality of life with high dose inhaled steroids, and this is the largest trial of these agents in patients similar to those seen in the clinics of physicians reading the Canadian Respiratory Journal. We cannot ignore these findings, especially when they are supported by the results of several other studies (4,7). It is, I believe, presently justifiable to give inhaled steroids to patients with a history of many exacerbations or to patients in whom one thinks that exacerbations may have catastrophic results. For good or ill, such patients make up a very large fraction of those seen by physicians reading the Canadian Respiratory Journal. Because of this, I think that we must maintain a certain skepticism about the value of this therapy. After all, we do not know the mechanisms involved in exacerbations and have no idea why inhaled steroids should affect patients in the absence of an effect on the basic disease process.

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REFERENCES