



# Through a glass darkly: inhaled corticosteroids, airway inflammation and COPD

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**ICS can reduce inflammation in COPD but this effect ceases after drug discontinuation; clinical effects are unclear** <http://ow.ly/JgwT306sFn2>

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It is 18 years since I last used the famous biblical phrase “through a glass darkly” to describe our uncertainties about the use of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) patients [1]. Subsequently, an enormous amount of research has been undertaken, which has clarified the role of ICS in clinical management [2]. There is general agreement that these drugs produce small improvements in lung function but that their main clinical benefit is to reduce exacerbation frequency, especially for events treated with oral corticosteroids [3]. The impact on COPD mortality of adding ICS to long-acting inhaled bronchodilators remains famously controversial, as does the potential of ICS to reduce the rate of decline of forced expiratory volume in 1 s (FEV<sub>1</sub>), the topic of my original editorial [1]. Recent data suggest that a small reduction in rate of decline may occur with ICS use [4], in keeping with meta-analysed data from previous studies [5]. The most important development has been the proposal that ICS are only beneficial in individuals with high normal blood eosinophil counts [6], although the threshold value to identify such an effect may reflect the level of background bronchodilator treatment [7].

In contrast, there is still considerable uncertainty about how ICS effect these changes in clinical outcome. The observation that lung function changes over a few weeks after ICS are stopped but exacerbation rates do not change subsequently [8] suggests that different mechanisms may underlie different effects attributable to these drugs. The reasonable assumption has been that ICS would work by suppressing inflammation but establishing that this is so has proven difficult. This reflects our lack of a clear definition of what constitutes an abnormal or excessive inflammatory response in COPD, our reliance on sampling of the central airways as a marker of inflammation in more peripheral parts of the lung, and variation in the predominant inflammatory cells in the airway wall and lumen over time and with disease severity. Despite these problems, investigators have shown that ICS (at least when combined with a long-acting  $\beta$ -agonist (LABA)) are associated with a reduction in luminal CD4<sup>+</sup> and CD8<sup>+</sup> cells and in sputum neutrophil, macrophage and monocyte numbers [9, 10]. These trials were relatively brief, lasting only a few months. The most ambitious and potentially most informative study of ICS and inflammation in COPD came from the combined efforts of the highly regarded groups in Groningen and Leiden (the Netherlands) who pooled their resources to conduct the GLUCOLD (Groningen and Leiden Universities Corticosteroids in Obstructive Lung Disease) study. This trial randomised corticosteroid-naïve patients with moderate spirometric impairment (mean post-bronchodilator FEV<sub>1</sub> 63% predicted) to receive the inhaled corticosteroid fluticasone propionate alone or with the LABA salmeterol for 30 months and compared the effect on airway inflammation to patients

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randomised to fluticasone propionate alone for 6 months or placebo. As expected, there were improvements in spirometry and symptoms and reductions in lymphocyte numbers while receiving ICS treatment [11].

Among the strengths of the GLUCOLD study was its extended duration and the inclusion of an arm where treatment was stopped. This has assumed greater importance in the light of research showing that ICS can be safely discontinued in both moderate and severe COPD patients [12, 13]. These conclusions were based on clinical outcomes, but what happens to the airway inflammation when this is done? In this issue of the *European Respiratory Journal*, KUNZ *et al.* [14] report an observational follow-up study of some of the GLUCOLD participants that begins to address this issue. They followed-up 85 participants in the original trial for a further 5 years and obtained data on 61 of these. The data on decline of lung function in this follow-up population have already been reported [15], but the authors add data from repeat biopsies 7.5 years after the original trial randomisation in 29 individuals and sputum data in 33. In line with current guidance, many patients did not receive ICS after the trial and using pharmacy records they found patients who were either given no ICS or took <50% of the prescribed doses. In this further subset of patients, when comparing fold-change in cell numbers, they found a significant increase in lymphocyte numbers in biopsies from those who had discontinued ICS after 2.5 years, a change paralleled by a rise in sputum inflammatory cells. In a very small number of subjects, there appeared to be some relationship between the change in post-bronchodilator FEV<sub>1</sub> and the change in cellularity of both biopsies and sputum.

The conclusion of KUNZ *et al.* [14] that use of ICS in COPD does not have a long-lasting effect seems very reasonable but inevitably there are limitations to this type of research. Although the smoking status data of the original group are included in table 1, the numbers smoking when the follow-up data were collected are not presented; more importantly, neither are the numbers who stopped or restarted smoking during follow-up. This could confound some of the conclusions drawn here, as is evident from a cross-sectional analysis of sputum samples and smoking status previously reported by this group [16]. KUNZ *et al.* [14] focus on the patients in whom ICS were discontinued but might have stressed the comparison with the larger follow-up group who received little or no ICS over 7.5 years. These data are in the supplement and suggest that for some cell lines, like CD8<sup>+</sup> lymphocytes, numbers of cells are very stable over time, while for others the change is relatively modest compared with the larger changes when ICS are stopped. Whether this means that inflammation in COPD is not progressive but simply persistent and whether regression to the mean has contributed to the large impact of ICS cessation is not clear. The authors did not see any relationship between the change in inflammation or lung function and the blood eosinophil count. Again, this may reflect the very small number of available observations, as a *post hoc* analysis of the ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe) study found that patients with >2% blood eosinophils had a slower decline in FEV<sub>1</sub> when treated with ICS [17].

So, has the glass through which we look at inflammation in COPD become any clearer? Yes ... but it is still a murky picture. It does seem that ICS can reduce central airway inflammation in COPD and that this effect wanes when these drugs are stopped. Whether this explains some or indeed any of the benefits of ICS treatment in COPD remains an open question, as does the issue of whether inflammation is causal or an important epiphenomenon in COPD. We will have to wait for more effective ways of normalising the inflammatory response in the airways and lung parenchyma, probably at an earlier stage in the natural history, before these more basic questions can be satisfactorily answered.

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