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# Inhaled Corticosteroids in COPD: A Controversy

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**Key Words**
Chronic obstructive pulmonary disease · Corticosteroids, inhaled · Long-acting $\beta_2$-agonist

**Abstract**
Inhaled corticosteroids (ICS) are now very widely used in high doses in the management of COPD patients. In sharp contrast to the situation in asthma, ICS provide little or no benefit in COPD patients and may have long-term detrimental effects. High doses of ICS fail to reduce disease progression or mortality, even when combined with a long-acting $\beta_2$-agonist (LABA). Several trials have demonstrated that ICS reduce exacerbations by 20–25%, particularly in patients with more severe disease, but these studies are confounded by poor trial design and more appropriate analysis shows no benefit. Indeed, the benefit of combination inhalers seems to be largely due to the effect of the LABA, and long-acting bronchodilators – including tiotropium – provide similar benefits in reducing exacerbations. However, there may be some COPD patients, for example those with concomitant asthma, who benefit from ICS. Yet it has not been possible to identify any clinical factors that predict corticosteroid responsiveness in COPD patients in the large clinical trials. There is increasing evidence that high doses of ICS may have detrimental effects on bones and may increase the risk of pneumonia. ICS fail to suppress inflammation in COPD patients because there is a marked reduction in histone deacetylase-2, the nuclear enzyme that corticosteroids require to switch off activated inflammatory genes. In the future, alternative anti-inflammatory treatments will be needed for COPD or therapeutic strategies which reverse the molecular pathways that causes corticosteroid resistance.



## Introduction

Inhaled corticosteroids (ICS) are highly effective in asthma and have become the mainstay of therapy in all patients with persistent symptoms [1]. This reflects the fact that asthma is associated with a chronic inflammation of the airways that is readily suppressed by low doses of corticosteroids in most patients [2]. In sharp contrast, corticosteroids are poorly effective in most patients with COPD, even when high oral or inhaled doses are used. Patients with COPD are commonly treated as if they have asthma and many patients with a diagnosis of COPD are now treated with high doses of ICS, often in

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combination with a long-acting $\beta_2$-agonist (LABA) as a fixed combination (fluticasone/salmeterol or budesonide/formoterol). Over 70% of patients with diagnosed COPD are now treated with high doses of ICS as a result of successful marketing, yet there is still little evidence for their clinical benefit, and increasing evidence that the high doses currently recommended are harmful and costly [3, 4]. ICS are recommended in currently used management guidelines for COPD; for example, the GOLD Guideline suggests that inhaled corticosteroids should be introduced only in patients with severe disease ($FEV_1$ <50% predicted normal, GOLD stage III) who have two or more exacerbations a year [5]. It is likely that this would amount to less than 20% of all patients, rather than the more than 70% currently prescribed this therapy, suggesting that ICS are grossly overprescribed. Indeed, the question is whether they should be used at all, unless patients have concomitant asthma [4].

### Clinical Trials with ICS

Many placebo-controlled clinical trials have been conducted with ICS in patients with differing severities of COPD. The first relatively small study showed no effect of high-dose ICS on $FEV_1$ decline in COPD patients over 2 years and no effect on exacerbations, although the study was underpowered to measure this [6]. A second study showed no clinical benefit of high dose ICS over 6 months [7]. Four large studies then looked at high doses of ICS compared to a placebo over a 3-year period and all showed no effect on disease progression, measured by annual decline in $FEV_1$, which was the primary outcome measurement of these studies [8–11]. However, there was a reduction in the number of exacerbations, a secondary outcome measure, in two of the studies, although there were differences in how exacerbations were defined. An earlier study specifically looked at exacerbations of COPD and showed that high-dose ICS had no overall effect on exacerbations, but a post-hoc analysis showed a reduction in severe exacerbations [12]. Even putting all these studies together in a meta-analysis failed to show any effect on $FEV_1$ decline [13], although another meta-analysis of the same data apparently showed a small reduction in disease progression [14]. None of these studies was sufficiently powered to look at mortality, but pooled analysis of several trials comprising over 5,000 patients suggested that there was a reduction in all-cause mortality of approximately 25% [15]. In the large TORCH study including approximately 6,000 patients with COPD studied over 3 years, in which all-cause mortality was the primary outcome measure, there was no evidence that high-dose fluticasone alone reduced mortality – in fact there was a small increase (~6%) in mortality by the end of the study, although this was not statistically significant [16]. A post-hoc analysis of the TORCH study showed that ICS has a small but statistically significant effect in reducing the annual rate in $FEV_1$ decline [17]. Taking all the studies together, a meta-analysis, which included over 13,000 COPD patients, found no significant effect if ICS on rate of $FEV_1$ decline or on mortality, although exacerbations were reduced by approximately 25% [18].

### LABA/ICS Combination Studies

More recently, the effects of fluticasone/salmeterol and budesonide/formoterol combination inhalers have been studied, but these studies are often difficult to interpret as it is difficult to disentangle the effect of the long-acting bronchodilator from the effect of the corticosteroid. These trials showed beneficial effects of the combination inhaler, but the effects of the ICS alone when used as a comparator were less marked or absent [16, 19–24]. Combination inhalers consistently reduce exacerbations by 20–25%, which is similar in magnitude to the effects of long-acting bronchodilators (LABA or tiotropium) alone. The largest of these studies, the TORCH study, showed a reduction in all cause mortality with fluticasone/salmeterol, which did not quite reach statistical significance ($p = 0.052$). A meta-analysis, which included the TORCH data, found no effect of combination inhalers on mortality, however [25]. Taken together, these data provide little evidence that ICS reduce disease progression or mortality, even when combined with LABA. However, there is a consistent reduction in exacerbations and hospitalisations, similar in magnitude to that seen with lung acting bronchodilators such as LABA and tiotropium. Indeed, a direct comparison of fluticasone/salmeterol and tiotropium in COPD patients showed no statistical difference in exacerbation rates over 2 years [26].

### Misinterpretation of the ICS Trials

Suissa et al. [27] have identified several shortcomings in the randomised controlled studies of ICS in COPD patients. A major limitation of these studies was the re-

quirement that patients should stop using their prescribed ICS at the time of randomisation, so that a large proportion of patients in the placebo or comparator arms were abruptly withdrawn from a high dose of ICS. A detailed re-analysis of one such trial showed that the effect of ICS on the likelihood of the first exacerbation was significantly protective *only* among patients who were previously treated with ICS but had to discontinue [27]. Furthermore, it showed no effect of ICS in patients who were naïve to ICS prior to randomisation. Thus, trials that have reported a benefit for ICS may have simply shown an effect of abruptly discontinuing high dose ICS therapy, which may lead to side-effects, such as relative adrenal insufficiency and other rebound steroid effects, since there are clear systemic effects with high doses of ICS such as fluticasone propionate.

Another problem that was identified was the incomplete follow-up of patients, who were observed only until they discontinued the study drug, rather than to the end of planned follow-up. This is a major problem in view of the high and early rates of discontinuation in these studies. This bias was demonstrated in studies with incomplete follow-up that found a ~25% reduction in all-cause mortality with ICS [15], which was not confirmed in the TORCH trial, in which all patients were followed for 3 years to identify all deaths using a proper intent-to-treat analysis [16]. The OPTIMAL trial, which also avoided this bias by identifying exacerbations, the primary outcome, for the entire one-year follow-up period also found no benefit of ICS [24].

Measurement of $FEV_1$ decline was also misinterpreted due to failure of intention-to-treat analysis. In the TORCH study, nearly 18% of placebo patients did not contribute a single $FEV_1$ value to the analysis of $FEV_1$ decline, compared with only 9% of patients allocated to combination therapy [17]. The excluded patients are likely to have had the lowest $FEV_1$ values at their initial visit, so that the slope of $FEV_1$ decline in the remaining patients with better $FEV_1$ initial values at the first visit may have been affected by regression to the mean, thus giving the impression that ICS affect $FEV_1$ decline [28].

As discussed above, an important issue with combination therapy in COPD patients relates to the effect of each component. A 2 × 2 factorial study analysis of the TORCH trial data to measure the independent contribution of the LABA and the ICS found that the reduction in mortality was entirely explained by the salmeterol component and none could be attributable to the ICS [27, 29].

Finally, observational studies that have suggested a reduction in mortality with ICS use were all flawed with 'immortal time bias' as there was a survival advantage to the ICS users by defining exposure in such a way that they had to be alive to receive their ICS prescription [30]. Indeed, a correct analysis of the data completely eliminated any apparent protective effect of ICS [31].

## Are There Any COPD Patients Who May Benefit from ICS?

COPD is a heterogeneous disease with several different pathological mechanisms, including emphysema, small airway disease and mucous hypersecretion, so it is possible that corticosteroids might work more effectively on some components of disease compared to others. However, this has so far not been investigated or proven in clinical trials. COPD patients who have some of the clinical features of asthma, with greater reversibility of airways obstruction, may have increased sputum eosinophils and an increase in exhaled nitric oxide concentration, which are characteristics of asthmatic airway inflammation [32]. These COPD patients probably have coexistent asthma. COPD patients with increased sputum eosinophils show a reduction in sputum eosinophils with oral steroids [33] and a management strategy that increased ICS dose or added oral steroids with increased sputum eosinophils reduced exacerbations, as had previously been observed in patients with asthma [34]. A meta-analysis of over 13,000 COPD patients failed to identify any clinical factors that were associated with better responsiveness to ICS [18].

## Adverse Effects of ICS in COPD Patients

ICS, especially in high doses, may cause oral candidiasis and hoarseness, and these local side effects are increased in COPD patients on ICS [18]. High doses of ICS are well known to have systemic effects due to lung absorption. Elderly patients with COPD who have poor mobility and nutrition, who smoke and have co-morbid diseases, such as ischaemic heart disease and diabetes, may be at greater risk of developing corticosteroid side effects, but these may take time to develop and this may be longer than the duration of a clinical trial, even over a 3-year period. Even low doses of ICS are associated with increased risk of cataracts in elderly patients [35]. There is a dose-related increase in the risk of fractures with use of ICS amongst elderly patients in the community [36]. Patients with COPD may be at even greater risk as COPD

itself is associated with osteoporosis, and cigarette smoking, immobility and poor nutrition are additional risk factors [37, 38]. In the Lung Health Study lumbar and hip bone density was reduced in the patients treated with inhaled triamcinolone but there was no increase in fractures [39]. However, in the TORCH study, although there was a high incidence of osteoporosis amongst COPD patients, there was no detrimental effect of ICS on bone mineral density or on fracture rate [40].

Recently, several large studies have shown that ICS (alone or in combination) are associated with a significant increase in risk of pneumonia, although this has not been well characterized [23, 26, 41]. This has been confirmed in a population-based study of over 175,000 COPD patients with hospital-diagnosed pneumonia, where there was a clear dose-related risk [42]. The increased risk of pneumonia with ICS has also been confirmed in meta-analyses, which have also identified an increased risk of death from pneumonia [18, 43, 44]. This increased risk of pneumonia with ICS may reflect the increased susceptibility of COPD patients to bacterial infections as a result of impaired mucosal innate immunity in the lungs. More studies are needed to define the pneumonia, the dose-relationship to ICS and whether there are differences between different corticosteroids.

### Why Do ICS Not Work in COPD?

There are now good scientific reasons why even high doses of ICS fail to reduce inflammation in COPD patients. This corticosteroid-resistance has been demonstrated by the failure of high doses of ICS to reduce inflammatory markers in sputum or bronchial biopsies of COPD patients [45–49]. The reason why ICS fail to suppress inflammation cannot be explained by impaired access of the inhaled drug to sites of inflammation as an oral corticosteroid is equally ineffective [45].

The reason for the extreme corticosteroid resistance in COPD may be due to a marked reduction in the nuclear enzyme histone deacetylase-2 (HDAC2), which is required for corticosteroids to switch off activated inflammatory genes that are associated with histone acetylation [50–52]. This molecular mechanism involves HDAC2 deacetylating acetylated glucocorticoid receptors to allow them to suppress nuclear factor-κB (NF-κB)-activated inflammatory genes [53]. The reduction in HDAC2 activity and expression appears to be secondary to oxidative stress through the formation of peroxynitrite, which nitrates certain critical tyrosine resides on HDAC2, leading to ubiquitination and destruction by the proteasome [54, 55]. In addition, oxidative stress activates phosphoinositide-3-kinase-δ (PI3Kδ), which also results in inactivation of HDAC2 [56]. The corticosteroid resistance persists even after smoking cessation, as the inflammatory response and oxidative stress continue [57, 58] and HDAC2 is just as reduced in ex-smokers as in smokers [51]. In asthmatics who smoke there is a marked reduction in responsiveness to corticosteroids [59] and this may also be explained by the oxidative stress of cigarette smoking reducing the anti-inflammatory effects of corticosteroids through a similar molecular mechanism involving HDAC2 [60].

### What Is the Way Forward?

Corticosteroid resistance in COPD is a major clinical problem in COPD patients at all stages of the disease [61]. It cannot be overcome by increasing the dose of ICS or by oral corticosteroids, and systemic side effects at these high doses are problematic. There are two possible approaches. The first is to develop alternative anti-inflammatory treatments, such as phosphodiesterase-4 inhibitors, p38 mitogen-activated protein kinase inhibitors or NF-κB inhibitors, which suppress inflammatory genes independently of HDAC2 [62]. These treatments all have a high risk of side effects after systemic administration so that inhaled delivery may be needed with drugs that are retained within the lung. The alternative approach is the reverse corticosteroid resistance by restoring HDAC2 activity and levels to normal. This can be achieved in vitro by viral plasmid transfer of HDAC2 [53], but gene transfer is unlikely to be a useful therapeutic approach. The same effect may be achieved with low concentrations of theophylline in vitro, particularly when HDAC2 is reduced by oxidative stress [63–65]. Similar effects are also seen in smoking mice in vivo [66] and in COPD patients [Ford et al., unpubl. data]. Low doses of theophylline also improve recovery from a COPD exacerbation and this is associated with an increase in HDAC activity [67]. Furthermore, low dose theophylline combined with ICS is more effective than either drug alone in improving lung function in smoking asthmatics [68]. The molecular mechanisms of action of theophylline in restoring HDAC2 activity and steroid responsiveness are currently being elucidated, but it seems that theophylline may achieve this by directly inhibiting oxidant-activated PI3Kδ and its effects

are mimicked by selective PI3Kδ inhibitors and by knocking out the PI3Kδ gene in mice [56]. Theophylline is cheap and available and when used in low doses (giving plasma concentrations of 1–5 mg/l) does not cause significant side effects. This therapy should be investigated in patients with COPD in long-term studies using important clinical outcomes, such as disease progression, exacerbations and mortality.

There are other strategies for reversing corticosteroid resistance in COPD, including more potent antioxidants and peroxynitrite scavengers [69]. Other drugs may inhibit the signalling pathways that lead to reduced HDAC2, including existing treatments such as macrolides [61, 70]. In the future novel activators of HDAC2 may be developed [71].

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