Eur Respir J 2009; 34: 10–12
DOI: 10.1183/09031936.00022809

PRO AND CON EDITORIALS

Inhaled corticosteroids in COPD: a case in favour

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Chronic obstructive pulmonary disease (COPD) is a heterogeneous disease, which is characterised by reduced post-bronchodilator lung function in all patients [1]. Although hyperresponsiveness and acute bronchodilator reversibility have been regarded as characteristics of asthma, it is now generally acknowledged that these clinical features are also present in COPD. Results as high as 39–66% for reversibility [2], dependent on the method of expression, and 60% for hyperresponsiveness, as measured with methacholine, have been reported. Patients generally show progressive lung function loss, accompanied by worsening respiratory symptoms and health status [1]. These clinical features are associated with airway inflammation, *i.e.* bronchial infiltration of neutrophils, macrophages, lymphocytes, and mast cells [3–5]. Smoking accelerates lung function loss and increases mortality in COPD, and smoking cessation has consistently been shown to improve these outcomes. Other risk factors for a worse prognosis include higher age, female sex, airway hyperresponsiveness, sputum production, underweight and frequent exacerbations [1]. As well as smoking cessation, it is logical to investigate whether treatment that changes these risk factors and/or their underlying mechanisms can also change the long-term outcome of COPD.

Many studies have assessed the long-term benefits of available COPD treatments, such as inhaled corticosteroids (ICS), long-acting β_2-agonists (LABA) and long-acting anticholinergics. As a result, current guidelines recommend treatment with ICS for patients with severe COPD and frequent exacerbations, in addition to long-acting bronchodilators for patients with moderate-to-severe COPD [1]. Below we summarise evidence advising the use of ICS or ICS+LABA in COPD from double-blind studies with intermediate (1–2 yrs) and long-term (>2 years) follow-up.

It is now clear that regular anti-inflammatory treatment with ICS improves symptoms, health status and forced expiratory volume in 1 s (FEV_1) while decreasing exacerbation rates [6–9]. Withdrawing ICS (under protection of LABA) in moderate-to-severe COPD results in deterioration of FEV_1, symptoms, health status and exacerbation rates [10, 11]. Furthermore, combining a LABA with an ICS provides additional improvements in exacerbation rates, health status and survival in moderate-to-severe COPD [12, 13].

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The debate now is whether ICS alone or combined with LABA changes FEV_1 decline and mortality in COPD as well. Initial studies have not generally suggested a beneficial effect on FEV_1 decline [6–9, 12, 14] but data from the much larger TORCH study (Towards a Revolution in COPD Health) indicates that prolonged therapy with ICS and/or LABA attenuates FEV_1 decline in COPD [15]. With respect to mortality, a meta-analysis of seven prospective studies with intermediate and long-term follow-up showed that mortality decreased with ICS treatment in COPD patients of all severity stages (stage I: 15%; II: 49%; III: 28%; and stage IV: 9%), an effect particularly significant in stages III and IV [16]. The TORCH study in >6,000 moderate-to-severe COPD patients did not support this finding, at least for ICS alone [13]. The issue of statistical power played a part in TORCH, since there was a statistical significance level of 0.052 between ICS+LABA treatment and placebo, probably reflecting the lower than expected mortality rate and high drop-out rate in the placebo group, many of whom received one of the trial treatments for most of the study.

ICS with or without LABA may influence FEV_1 decline directly or indirectly *via* exacerbation rates, but also *via* airway hyperresponsiveness, an established risk factor for accelerated FEV_1 decline [17, 18]. One study assessing hyperresponsiveness in mild-to-moderate COPD [10] showed that hyperresponsiveness improved but FEV_1 decline was unaffected. Another study of 6-month duration did not show significant improvements in methacholine hyperresponsiveness with ICS. However, this study excluded patients whose symptoms or lung function deteriorated after discontinuation of treatment, thereby reducing the signal for improvement [19]. The recent GLUCOLD study provided new data in steroid-naïve patients (submitted for publication). It showed that a 30-month ICS maintenance therapy with or without LABA in moderate COPD reduces the rate of FEV_1 decline and improves hyperresponsiveness and dyspnoea [20]. The effect was unaffected by smoking, refuting an argument often used as a reason not to introduce ICS treatment in COPD. In general, a drug is regarded as being effective when health improves after it is introduced and deteriorates when it is withdrawn. ICS fulfils this criterion as patients in the GLUCOLD study improved after ICS treatment started, while FEV_1 decline and bronchial hyperresponsiveness worsened in those randomised to treatment cessation after 6 months. Moreover, inflammation, which is thought to contribute to disease development and/or progression [3–5], increased in patients who stopped ICS treatment. Thus, the literature now provides good evidence that long-term ICS treatment modifies the disease progression by reducing the accelerated FEV_1 decline and improving

hyperresponsiveness, respiratory symptoms, exacerbations and health status.

How then can we reconcile differences between the early and later studies of lung function loss in COPD? Results might differ depending on the type of patients studied. The GLUCOLD study investigated steroid-naïve patients thereby excluding patients with unknown previous benefits from ICS, and avoiding the problem of selective drop-out in the placebo group. This cannot fully explain the benefits observed in the TORCH dataset, since almost half of the participants in each arm of the trial had used ICS before randomisation. Disease heterogeneity might also influence the outcome: the GLUCOLD study investigated predominantly steroid-naïve patients and most demonstrated hyperresponsiveness and/or modest FEV_1 reversibility. Studies showed that these characteristics, previously attributed to asthma, can be components of COPD [9, 17, 18, 20, 21]. This COPD phenotype may be particularly sensitive to ICS and its identification fits into the current focus on personalised medicine.

Clinical benefits of ICS with or without LABA in COPD may be mediated, at least partially, by their anti-inflammatory efficacy as assessed in airway wall biopsies. Short-term (2–3 months) ICS treatment in moderate COPD reduced bronchial mast cell numbers, but not $CD8^+$ cells, neutrophils or macrophages [22]. Combining ICS and LABA for 3 months provided anti-inflammatory effects *versus* placebo [23] and additionally reduced bronchial $CD8^+$ cells and macrophages compared with ICS monotherapy [24]. Treatment for 30 months provided sustained suppressive effects on bronchial T-lymphocytes and mast cells and inflammation returned when ICS treatment was stopped after 6 months [25]. These findings indicate that long-term ICS therapy in steroid-naïve patients with moderate COPD can reduce both the decline in lung function and airway inflammation. Although a short-term study showed beneficial anti-inflammatory effects of ICS+LABA over ICS alone [24], the GLUCOLD study showed that these effects were not long lasting [25]. Thus, beneficial effects of LABA combined with ICS on FEV_1 decline may operate by other mechanisms.

This interpretation of ICS effects is sometimes questioned and arguments against ICS range from absence of effects on sputum inflammation and FEV_1 to incorrect trial methodology [26, 27]. In some short-term smaller studies, particularly those using induced sputum, corticosteroid treatment has not modified plausible markers of COPD inflammation [28]. However, failure to change a selective biomarker does not mean that a therapy does not work. Moreover, studies have shown that ICS with or with out LABA may not affect sputum inflammation but have an effect on airway wall biopsies in conjunction with other clinical benefits [25]. The suggestion that ICS have an unimportant effect on post-bronchodilator FEV_1 seems hard to accept when several trials have shown that inhaled corticosteroids improve this outcome to a similar degree to that seen with long-acting bronchodilators [13, 29]. Other studies have criticised the trial methodology used in previous studies, either in terms of study design or analysis of exacerbation frequency. Clearly, the early reports which used simple nonparametric methods to express exacerbation rates were flawed, but more sophisticated analytical models are now available and, when applied to the earlier data, do not change the results [30]. In this context, plausible but inaccurate critiques of trial designs [27] can confuse the nonexpert reader and leave them with the impression that ICS were ineffective when they were in fact working.

When treating COPD, one has to consider the potential risks of ICS in COPD. The systemic availability of currently used ICS is low, given the low incidence of adrenal suppression in long-term studies [13]. Database studies suggest a measurable risk of osteoporosis and cataracts in patients who use ICS [31, 32] but the high background rate of these complications in COPD patients, irrespective of prior therapy, complicates interpretation of these data. Furthermore, serial data show no evidence that these complications occur more frequently with ICS use, at least over 3 yrs [13]. Pneumonia is diagnosed more often in COPD patients treated with ICS and in combination with a LABA [13] but, surprisingly, patients treated with ICS+LABA have a lower mortality, fewer exacerbations and better health status than those using long-acting bronchodilator drugs. Identifying patients at risk of developing pneumonia during ICS treatment is an important goal for the future.

What other challenges remain after these studies? The mechanisms underlying the beneficial effects remain unclear, *i.e.* do they work through a direct effect on inflammatory cells or indirectly through epithelial restoration or improvement in repair mechanism of the extracellular matrix? Mast cell inflammation appears to be more prominent in peripheral than central airways in COPD and so treatment with small particle size ICS might be even more effective in COPD. A double-blind study showed that hyperinflation improved more with small particle than large particle size ICS [33]. Another problem is the heterogeneity of COPD, with various degrees of emphysema and airway disease in different patients. Whether ICS treatment affects these various COPD phenotypes differently needs further investigation.

In summary, COPD can now be considered as a treatable disease. ICS used alone or in combination with LABA have beneficial effects on respiratory symptoms, health status and exacerbation rates in patients with moderate-to-severe COPD. These findings have been shown across the range of COPD severity, and the combination of ICS and LABA produces consistently better results than either drug used alone. Recent data suggests that disease progression, expressed as the change in lung function over time, is also modified by ICS containing regimes and that the time to a clinically significant deterioration in health status is delayed in symptomatic patients. There is a real opportunity to develop personalised medicine since these drugs decrease airway inflammation in conjunction with a reduction of FEV_1 decline in corticosteroid-naïve subjects with bronchial hyperresponsiveness and moderate COPD. These effects occur soon after treatment begins and stop when it is withdrawn, providing supportive evidence that disease modification at a cellular, physiological and clinical level is possible when these therapies are used. The improvements achieved are modest compared with the dramatic effect ICS have in asthma but are nonetheless clinically worthwhile. Today, there should be no defeatism in the management of COPD and patients should not be denied the benefits which these agents undoubtedly afford them.

STATEMENT OF INTEREST

Statements of interest for D.S. Postma and P. Calverley can be found at www.erj.ersjournals.com/misc/statements.dtl

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