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Seretide withdrawal increases airway inflammation in moderate COPD patients

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Introduction

Inhaled corticosteroids (ICS) are widely used to treat patients with chronic obstructive pulmonary disease (COPD), either alone or in combination with a long-acting beta agonist (LABA) [1]. Clinical trials of the effects of these drugs in COPD usually allow patients to be recruited irrespective of their previous ICS and/or LABA use [2]. In the subset of patients who are using ICS/LABA treatments, these are withdrawn at the start of the run-in period prior to randomisation to ensure that all patients in the study are at a similar baseline point [3]. However, it is probable that the withdrawal of medication in some patients causes clinical deterioration, which may continue if they are assigned to the placebo arm of the study. This is not clinically justifiable in some patients with severe or very severe COPD [Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage III–IV] [1]. However, in stable moderate COPD patients (GOLD stage II), ICS / LABA withdrawal is likely to be better tolerated, as these patients have better lung function. Nevertheless, it is possible that a significant clinical deterioration could occur, even in moderate COPD patients.

We hypothesised that ICS/LABA withdrawal would cause significant deterioration in clinical status and increase airway inflammation even in stable, moderate

GOLD stage-II COPD patients. We conducted a pilot study in 14 COPD patients using an open, parallel group design. Patients were randomised at a ratio of 3:2, stratified according to current smoking status, to either withdrawal or continuation of inhaled fluticasone propionate/salmeterol (SFC) for 6 weeks. Patients performed spirometry and sputum induction at randomisation (V0) and at 2-week intervals up to 6 weeks (V1, V2, V3). Inclusion criteria at screening were postbronchodilator forced expiratory volume in 1 s (FEV₁ 50–80% predicted and FEV₁/forced vital capacity (FVC) < 70%, stable dose of fluticasone propionate 500–1,000 µg per day and salmeterol 100 µg per day, current or ex-smokers with at least 10 pack years. In order to avoid potential severe exacerbations in patients randomised to withdrawal of SFC, the following patients were excluded: patients with a history of more than one exacerbation of COPD during the past 12 months requiring treatment with oral corticosteroids, or any previous admission for exacerbation of COPD requiring noninvasive or endotracheal intubation or admission to the intensive care unit. All patients provided written informed consent, and the study was approved by Central Manchester Research Ethics Committee and the Medicines and Healthcare Products Regulatory Agency (trial registration: www.controlled-trials.com/ISRCTN50541811).

Nine patients were randomised to the withdrawal group (mean age 65, four current smokers, mean pack years 54, mean percent predicted FEV₁ 68), and five were randomised to the continuation group (mean age 71, one current smoker, mean pack years 52, mean percent predicted FEV₁ 67). Four patients in the withdrawal group withdrew from the study due to exacerbation of COPD. Data from these patients are brought forward from the last observation obtained. There were no exacerbations in the

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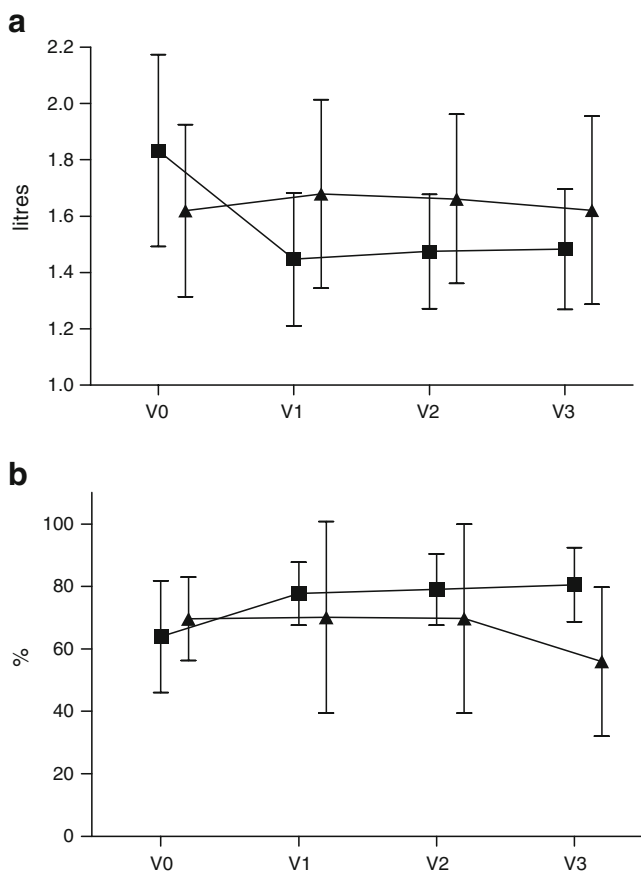


Fig. 1 Mean (95% confidence intervals) **a.** FEV₁ (forced expiratory volume in 1 s; **b.** Neutrophil percentage (%) in withdrawal (■) and continuation (▲) groups

continuation group. At 6 weeks (V3), there was a significant decrease in FEV₁ (0.35 L, $p=0.017$) and increase in sputum neutrophil percentage (16.5%, $p=0.03$) compared with V0 in the withdrawal compared with the continuation group (Fig. 1).

This pilot study shows that SFC withdrawal increases airway inflammation in moderate COPD patients without a recent history of exacerbations. Long-term clinical trials may consider it safe to withdraw SFC treatment from stable patients, but our data shows that this leads to an increase in airway neutrophils, a decrease in FEV₁ and more exacerbations.

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