



# Lung function changes over time following withdrawal of inhaled corticosteroids in patients with severe COPD

*To the Editor:*

The combination of an inhaled long-acting  $\beta_2$ -agonist with an inhaled corticosteroid (ICS) is widely used in the management of chronic obstructive pulmonary disease (COPD), primarily to prevent exacerbations [1]. Concerns about the increased risk of pneumonia, even with newer ICS [2], have generated interest in whether the ICS can be safely withdrawn from patients with COPD. We recently reported, in the WISDOM (Withdrawal of inhaled steroids during optimized bronchodilator management) study (clinicaltrials.gov identifier number: NCT00975195), that patients who continued treatment with a long-acting  $\beta_2$ -agonist plus a long-acting muscarinic antagonist did not have an increased risk of exacerbations [3]. However, we observed a statistically significant difference in forced expiratory volume in 1 s (FEV<sub>1</sub>) after complete ICS withdrawal and at the end of the study in favour of continued ICS treatment.

Here we present data on the time course of lung function in the WISDOM study before, during and after ICS withdrawal using the results of daily home-based spirometry. With daily measurements of lung function, we aimed to explore the time course of the change in lung function in more detail. Some of the results from this study have been previously reported in the form of an abstract [4].

The WISDOM study methodology and results have been published previously [3, 5]. Briefly, following a 6-week run-in on a combination treatment with long-acting  $\beta_2$ -agonist/long-acting muscarinic antagonist/ICS (salmeterol/tiotropium/fluticasone propionate), patients with COPD were randomised to either continue this treatment or have the ICS withdrawn in a stepwise manner over 12 weeks.

Lung function change was measured using spirometry (EasyOne; NDD Medical Technologies, Chelmsford, MA, USA, and Zurich, Switzerland) performed by trained staff during clinic visits and, following suitable training, by the patients themselves each day throughout the 52-week study. In the clinic lung function was assessed post-bronchodilator at the screening visit where patients were allowed to take their medication in the morning. The baseline value for lung function was assessed pre-bronchodilation at the randomisation visit. After randomisation, the first step-down in ICS dose from 500 to 250  $\mu\text{g}$  twice daily took place in the group who discontinued ICS.

Predefined end-points included changes from baseline to study weeks 6, 12, 18 and 52 in trough FEV<sub>1</sub> (measured in the clinic), and changes from baseline to study weeks 6, 12, 18, 27, 36, 45 and 52 in weekly mean FEV<sub>1</sub>, measured by home spirometry in the 7 days before the corresponding clinic visit. These end-points were analysed using a restricted maximum likelihood-based repeated measures approach adjusting for baseline FEV<sub>1</sub>. To determine the comparability of in-clinic and home-based spirometric data, a *post hoc* Bland–Altman analysis was performed to establish the level of agreement between these measurements.

A *post hoc* exploratory analysis of 46 consecutive weeks of home-based spirometric data was also undertaken. The 6 weeks immediately before the study week 12 clinic visit (ICS reduction from 250  $\mu\text{g}$  to 100  $\mu\text{g}$  twice daily) were designated as weeks –6 to –1 and the 40 weeks immediately after complete ICS withdrawal as weeks 1 to 40. For each week, the weekly mean FEV<sub>1</sub> for each patient was calculated if there were at least four measurements during the 7-day week, with no imputation for missing data. A separate analysis of covariance with terms for treatment and baseline FEV<sub>1</sub> was performed on the change from baseline at each week and the adjusted means presented graphically for each treatment group. The rates of change in FEV<sub>1</sub> from week 6 to week 40 (stable phase 6 weeks after the last change in treatment) were compared using a random-effects model adjusting for baseline FEV<sub>1</sub>.

A total of 2488 patients were randomised to study treatment and 2027 completed the study. Baseline in-clinic spirometry data were available for 2441 patients (n=1223 randomised to continued ICS treatment, and n=1218 to ICS withdrawal). The treatment groups were generally well matched in terms of baseline demographic and clinical characteristics. The Bland–Altman analysis of the overall study period showed good agreement between home-based and in-clinic data with a mean difference of between 40 and 50 mL that was consistent over time.

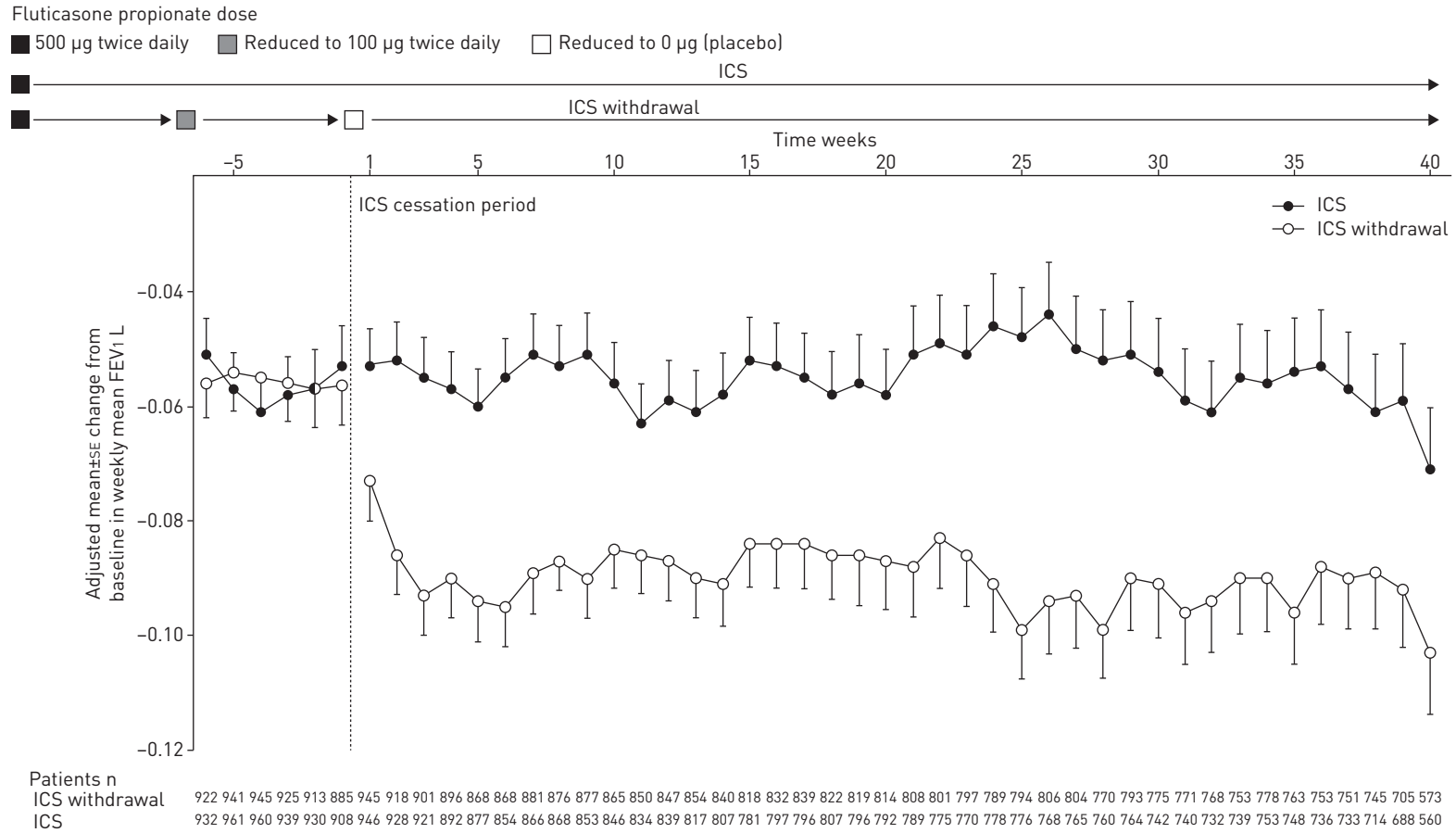


FIGURE 1 Adjusted mean±SE change from baseline in on-treatment weekly mean forced expiratory volume in 1 s (FEV<sub>1</sub>) 6 weeks before and 40 weeks after complete inhaled corticosteroid (ICS) withdrawal. The timeline for the figure is anchored to clinic visit 5, the point at which ICS therapy was discontinued. Therefore, the weeks shown in the figure correspond to the time before or after study week 12 and do not correspond to actual study weeks. Week -1 corresponds to the home-based data gathered the week prior to withdrawal and weeks 1-40 correspond to the weekly home-based data gathered after ICS discontinuation. Only patients with home-based data after ICS withdrawal have been included. The total number of patients included in the analysis who contributed a weekly mean for at least one of week 1 to week 40 after ICS withdrawal was 2135 (1066 in the ICS group, and 1069 in the ICS withdrawal group).

Analysis of the predefined end-points showed a decrease in weekly mean FEV<sub>1</sub> in the ICS-withdrawal group starting ~6 weeks after complete withdrawal of ICS. The adjusted mean treatment differences in on-treatment weekly mean FEV<sub>1</sub> were 4 mL and 6 mL at study weeks 6 and 12, when patients were on medium- or low-dose ICS, respectively, increasing to 42 mL at study week 18 ( $p < 0.001$ ). The treatment difference remained statistically significant at subsequent visits, ranging from 36 mL at study week 27 to 48 mL at study week 52, compared with the in-clinic difference in trough FEV<sub>1</sub> at study week 52 of 43 mL. The *post hoc* analysis revealed that the decrease in FEV<sub>1</sub> observed in the ICS withdrawal group started in the first week following complete withdrawal of ICS and continued for a further 2 weeks (fig. 1), after which FEV<sub>1</sub> stabilised. During the stable phase from week 6 to week 40 after ICS withdrawal, no further decrease in FEV<sub>1</sub> was observed in the ICS withdrawal group and the slopes of FEV<sub>1</sub> in the two groups were similar ( $p = 0.408$ ).

Our study design has strengths and limitations. Strengths include the large sample size and the use of weekly mean FEV<sub>1</sub> values based on at least four data points, which helped to overcome the impact of day-to-day variability. Potential limitations of this analysis of home-based spirometry are its *post hoc* nature and the potential unreliability of estimates of weekly mean FEV<sub>1</sub> based on four unsupervised home readings per week. However, the overall numbers of weekly mean FEV<sub>1</sub> values for the period of interest (weeks 1–40 after ICS withdrawal) were similar for the two treatment groups over time, allowing valid comparisons to be made between them.

Starting ICS treatment has been shown to result in a small but significant increase in post-bronchodilator FEV<sub>1</sub> compared with placebo or a long-acting  $\beta_2$ -agonist [2, 6, 7]. Conversely, withdrawing ICS treatment is associated with a fall in the in-clinic measurements of FEV<sub>1</sub> and worsening of symptoms [8, 9]. Our analysis shows that lung function can be maintained with low doses of ICS and that ICS withdrawal was associated with a nonprogressive reduction in lung function within 3 weeks of complete withdrawal. Thereafter, the change in spirometry over time was not different to that seen in patients still taking an ICS. Moreover, patients who continued to take an ICS had a similar disease course in terms of lung function to those who withdrew from ICS treatment. Although lung function worsened, the change was small, not progressive and did not predict clinically important changes, at least over the follow-up period of this study.



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**Decreased FEV<sub>1</sub> after complete ICS withdrawal in severe COPD was not progressive and did not predict clinical changes** <http://ow.ly/TYDv>

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## Bacteraemia in outpatients with community-acquired pneumonia



To the Editor:

Community-acquired pneumonia (CAP) is a frequent cause of morbidity and mortality worldwide. Approximately 20% of CAP patients require hospital admission [1, 2], leaving a large percentage of patients treated in the community as outpatients. In addition, bacteraemia is associated with worse outcomes, such as a higher prevalence of intensive care unit (ICU) admission and longer length of stay. Current international guidelines [1, 3, 4] do not recommend blood cultures as part of routine microbiological tests in patients managed in the community. However, there is little information regarding the prevalence and clinical impact of bacteraemia in CAP patients treated outside the hospital. Previous studies reported incidences of 2.1–7%, respectively [5–8]. However, few data exist regard predictive factors and the clinical outcomes associated with positive blood cultures in this population [8]. The current study aimed to determine the predictive factors and the clinical outcomes of bacteraemic outpatients with CAP, and describe their clinical, epidemiological and microbiological characteristics.

We performed a prospective study in Hospital Clinic of Barcelona, Barcelona, Spain. The study population consisted of adults aged 16 years or older, consecutively admitted to the emergency room with a diagnosis of CAP and discharged (within 12 h) for ambulatory treatments, from January 2000 to July 2014. We analysed all patients with available blood cultures (we drew four samples, two from the arm (anaerobic and aerobic); the following vials were used: the resin-containing BACTEC plus Aerobic/F and BACTEC plus Anaerobic/F, and the non-resin-containing BACTEC Standard/10 Aerobic/F and BACTEC Lytic/10 Anaerobic/F (BD, Madrid, Spain)). Contaminants were considered as a negative blood culture. Exclusion criteria are presented in the footnote of table 1.

During the study period, 6086 patients were admitted with a diagnosis of CAP. Of these, 687 (11% of total CAP) were treated as outpatients. 315 (46%) patients had no blood cultures. The study population therefore comprised a total of 372 (54%) patients treated as outpatients; 26 (7%) out of these 372 had bacteraemia. Both groups had similar baseline characteristics (table 1), except for bacteraemic patients having a higher proportion aged 50 years or over and pleuritic pain on presentation of pneumonia, and higher median levels of C-reactive protein ( $24.9 \text{ mg-dL}^{-1}$  (interquartile range 15.4–29.0  $\text{mg-dL}^{-1}$ ) versus  $12.4 \text{ mg-dL}^{-1}$  (6.7–21.1  $\text{mg-dL}^{-1}$ );  $p=0.001$ ) and white blood cell count on admission. There were no differences between the two groups on admission according to the CURB-65 (confusion, urea  $>7 \text{ mmol-L}^{-1}$ , respiratory rate  $\geq 30$  breaths per min, systolic blood pressure  $<90 \text{ mmHg}$  or diastolic blood pressure  $\leq 60 \text{ mmHg}$ , age  $\geq 65$  years) and Pneumonia Severity Index (PSI) scores. None of the patients with bacteraemia was readmitted, presented treatment failure or died. 30-day mortality was 0%.

Aetiological diagnoses were established in 124 (33%) cases. The most frequently isolated pathogen was *Streptococcus pneumoniae* (62 (50%) patients). The remaining microorganisms are presented in the footnote of table 1. Microorganisms isolated in bacteraemic cases were *S. pneumoniae* (24 (92%) patients) and *Haemophilus influenzae* (two (8%) patients). The most frequent serotypes in bacteraemic cases were 1, 19A, 3, 6A, 7F, 11A, 10A and 13.

Patients with bacteraemic CAP received the following antibiotics: fluoroquinolone monotherapy ( $n=15$ , 58%), a  $\beta$ -lactam plus a macrolide ( $n=6$ , 24%), a  $\beta$ -lactam plus a fluoroquinolone ( $n=1$ , 4%), a fluoroquinolone plus