



EDITORIAL

Are COPD patients with pneumonia who are taking inhaled corticosteroids at higher risk of dying?

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In 2007, CALVERLEY *et al.* [1] reported the results of the TORCH (Towards a Revolution in Chronic Obstructive Pulmonary Disease Health) study, which showed that combination of salmeterol (a long-acting β -agonist (LABA)) plus fluticasone propionate (an inhaled corticosteroid (ICS)) had a trend toward a lower all-cause mortality rate in patients with chronic obstructive pulmonary disease (COPD) compared with the placebo group, with a hazard ratio of 0.825 (95% CI 0.68–1.002; $p=0.052$). Despite the beneficial effects of ICS therapy in COPD patients, the results raised a possible safety issue regarding higher rate of community-acquired pneumonia (CAP) in the ICS groups. The probability of having pneumonia was higher among subjects receiving medications containing ICS (19.6% for ICS plus LABA and 18.3% for ICS alone) compared with the placebo group (12.3%; $p<0.001$) [1]. This association between ICS and pneumonia in COPD patients has also been seen in other studies: one study that examined the potential benefit of ICS and LABAs in reducing COPD mortality [1], and another comparing COPD exacerbation rates between patients receiving either salmeterol or the combination with a LABA [2, 3]. A follow-up evaluation of the TORCH study identified several risk factors associated with pneumonia, including age ≥ 55 yrs, forced expiratory volume in 1 s $<50\%$ predicted, COPD exacerbation in the year prior to the study, worse Medical Research Council dyspnoea score and body mass index $<25 \text{ kg}\cdot\text{m}^{-2}$. However, mortality rate due to pneumonia was not increased among subjects treated with ICS plus LABA, but the same could not be concluded for ICS monotherapy [4]. Therefore, it was suggested that ICS use increases the risk of CAP in COPD patients; however, the CAP severity event may be milder, and it is possible that these patients could have better clinical outcomes, as suggested by MALO DE MOLINA *et al.* [5].

In this issue of the *European Respiratory Journal*, SINGANAYAGAM *et al.* [6] examine the issue of the impact of ICS use on outcomes in COPD patients with pneumonia. The authors conducted a prospective observational study of patients with

spirometry-confirmed COPD presenting with a primary diagnosis of CAP. Outcomes were 30-day and 6-month mortality, need for mechanical ventilation and/or inotropic support, development of complicated pneumonia, time to reach clinical stability, and length of hospital stay. Over a 5-yr period, the investigators enrolled 490 patients with COPD and CAP. Most patients (76.7%) used ICS at the time of enrolment. According to the Global Initiative For Chronic Obstructive Lung Disease (GOLD) classification [7], most ICS users were stage III–IV. In contrast, more than half of non-ICS users were GOLD stage I–II. When ICS users were compared with non-ICS users, there were no statistically significant differences in outcomes, even after adjustment for COPD severity and Pneumonia Severity Index (PSI) score [8]. The authors concluded that prior ICS use was not associated with differences in clinical outcomes in COPD patients hospitalised with CAP.

The strengths of the study by SINGANAYAGAM *et al.* [6] are the prospective data collection design in a cohort of patients with spirometry-confirmed COPD, the stratification according to the GOLD guidelines, and CAP diagnosis by signs, symptoms and imaging studies. These are significant advances over prior studies of COPD patients and pneumonia. Another strength is the well-characterised cohort of hospitalised patients with CAP, with disease severity assessment at the time of clinical presentation using PSI [8] and CURB-65 scores (confusion, urea $>7 \text{ mmol}\cdot\text{L}^{-1}$, respiratory frequency $\geq 30 \text{ breaths}\cdot\text{min}^{-1}$, systolic blood pressure $<90 \text{ mmHg}$ or diastolic blood pressure $\leq 60 \text{ mmHg}$, and age ≥ 65 yrs) [9]. In addition, the evaluation of a wide range of important clinical outcomes is meritorious.

The results observed by SINGANAYAGAM *et al.* [6] contrast with those we reported previously [5]. We used a US Dept of Veterans Affairs administrative cohort of hospitalised patients with pneumonia and assessed the association of ICS exposure with mortality [5]. Of 6,353 patients diagnosed with pneumonia and with a prior history of COPD, 38% were receiving ICS at the time of admission; multilevel regression models showed lower 30- and 90-day mortality (OR 0.76 (95% CI 0.70–0.83) and OR 0.80 (95% CI 0.75–0.86), respectively) for outpatient ICS users. We concluded that these data suggested a potential beneficial effect, or at least not a deleterious effect, of the outpatient use of ICS in COPD patients who developed pneumonia. The major limitation of our study was that we did not have spirometric confirmation of COPD and lacked complete data for severity of illness adjustment.

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SINGANAYAGAM *et al.* [6] attempted to address several of these issues. Can we conclude that this study has addressed all of the methodological concerns to finally state that COPD patients who receive ICS and develop pneumonia do not have worse clinical outcomes? We believe there are several limitations that will require further research. First, the small sample size may be insufficient to detect a significant difference in mortality, as demonstrated by their small effect size and wide 95% confidence intervals. This is why most of the recently published large COPD studies included $\geq 6,000$ subjects.

Secondly, are all ICSs equal? The authors did not describe differences related to the type of ICS, duration of outpatient therapy, ICS dose prior to clinical presentation and their relationship with clinical outcomes. These data are crucial and their absence is an important limitation of the study. Furthermore, some studies suggested that there are differences related to the type of ICS and risk associated with CAP. A recent meta-analysis of individual patient data published by SIN *et al.* [10] suggested that budesonide treatment for 12 months did not increase the risk of pneumonia in COPD patients, contrary to the data published with fluticasone in the TORCH study [1].

Thirdly, the dose effect of ICS may impact on adverse events, as suggested by ERNST *et al.* [11], and was not described in the study by SINGANAYAGAM *et al.* [6]. ERNST *et al.* [11] described a two-fold increased risk of CAP-related hospitalisation with higher doses of fluticasone propionate ($\geq 1,000 \mu\text{g}\cdot\text{day}^{-1}$).

In addition, several other issues need to be clarified. It is unclear why 23% of the patients in GOLD stage I–II received ICS. The GOLD guidelines recommend the use of ICS in patients in GOLD stages III–IV or patients with frequent exacerbations [7].

The authors also did not address the issue related to using systemic (oral or intravenous) corticosteroids at the time of clinical presentation, which is common practice in the real world. It is unclear if a significant bias favouring the patients that were receiving ICS was driven by the use of systemic corticosteroids when the COPD patients were admitted with pneumonia.

There is also no description of how many patients were continued on ICS during hospitalisation and/or were discharged on ICS. Relevant information regarding COPD patients who received long-acting anticholinergics, such as tiotropium, would have also strengthened the study. WEDZICHA *et al.* [3] assessed the relative efficacy of LABA plus ICS with the long-acting bronchodilator tiotropium in preventing COPD exacerbations and related outcomes in severe and very severe COPD patients. Beneficial effects were observed for the ICS plus LABA group, with better health status and lower death rate. However, more pneumonias were reported in the ICS plus LABA group compared with tiotropium (8 *versus* 4%; $p=0.008$). In addition, WELTE [12] assessed the efficacy of ICS plus LABA with tiotropium in patients eligible for ICS/LABA combination therapy. Those authors concluded that budesonide/formoterol with tiotropium *versus* tiotropium alone provided rapid and sustained improvements in lung function, health status, and morning symptoms and activities, and reduced exacerbations. There

were only three cases of pneumonia within each treatment group (<1%), which is consistent with prior studies [13–15].

Finally, the authors needed to address other variables that are associated with poor clinical outcome (*i.e.* mortality), such as microbiology, appropriate/adequate antibiotic therapy, prior influenza, pneumococcal vaccination, *etc.*

Although there is some evidence that ICS use in COPD patients may increase the incidence of CAP, most studies have failed to show an impact on outcomes. Clinicians should use these medications judiciously and, at the same time, be aware that the frequency of CAP may be increased. However, we can be reassured that there is little support for the hypothesis that ICS use associated with CAP increases mortality risk in COPD patients. Additional research is needed to address the limitations of this and other studies, and to determine the safety profile of ICS in COPD patients.

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STATEMENT OF INTEREST

Statements of interest for all authors can be found at www.ersjournals.com/site/misc/statements.xhtml

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