EDITORIAL

Inhaled corticosteroids and survival in chronic obstructive pulmonary disease

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Chronic obstructive pulmonary disease (COPD) is a major cause of mortality worldwide [1]. In the majority of cases, the diagnosis is made relatively late in the natural history of the disease. These patients will endure years of progressive dyspnoea with consequent gradual reduction in their functional capacity, restriction to their performance of the activities of daily living, or, even worse, a limit to their fulfilment of a normal role at work and/or at home. The slow progression of the disease is punctuated by acute exacerbations that require medical attention and may result in mortality.

The goals in the management of COPD are to prevent and/or treat acute exacerbations and to improve the long-term course of the disease. The strategies available to achieve these goals include smoking cessation, rehabilitation, self-management, and pharmacological treatment. Smoking cessation is the single most effective way to reduce the risk of developing COPD and stop its progression [2]. Self-management [3] and rehabilitation [4] have also been shown to reduce hospitalisation [3, 5] and improve quality of life [3–5]. Of the pharmacological therapies, bronchodilators are well established as effective symptomatic therapy [6]. Based on recent controlled trials [7], it has been demonstrated in patients with advanced COPD that inhaled corticosteroids can reduce exacerbation rate without significantly modifying the rate of decline of lung function. The benefits of inhaled corticosteroids in improving long-term prognosis, such as mortality, are still under investigation.

In this issue of the *European Respiratory Journal*, SIN and MAN [8] report that any prescription of inhaled corticosteroids was associated with a 25% reduction in all-cause mortality (relative risk (RR): 0.75; 95% confidence interval (CI): 0.68–0.82) in a cohort of 6,740 patients with advanced COPD in Alberta, Canada. The impact of inhaled corticosteroids on pulmonary specific-cause mortality was also associated with a 30% risk reduction (RR: 0.80; 95% CI: 0.53–0.93). Hospital discharge data from the healthcare database were used to identify patients ≥ 65 yrs old, who were recently hospitalised for COPD. The key findings of the present study were a reduction of mortality over a 3-yr period and a dose/response relationship. Patients who had received intermediate

doses (501–1,000 $\mu\text{g}\cdot\text{day}^{-1}$ of beclomethasone or equivalent) or high doses ($>1,000 \mu\text{g}\cdot\text{day}^{-1}$) of inhaled corticosteroids had greater reduction in mortality than those who had received the lower dose ($\leq 500 \mu\text{g}\cdot\text{day}^{-1}$) therapy. These findings are consistent with those described by SIN and TU [9], who used similar population and methodology in a database from Ontario in Canada and showed a 29% reduction in all-cause mortality over 1 yr. They are also in agreement with a recent report by SORIANO *et al.* [10] who showed that regular use of fluticasone propionate alone and in combination with salmeterol was associated with increased survival of COPD patients using the UK General Practice Research Database. Although all three studies have found consistent results, all three were conducted using the same research design and similar sources of data.

Pharmacoepidemiological studies such as these can be considered useful complements to randomised clinical trials and can provide useful findings for new hypothesis testing. However, as mentioned by the authors of the present study, it is important to recognise that observational studies are much more susceptible to confounding and biases than randomised controlled trials [11].

What are some of the limitations of these large database studies? First, there may be diagnostic misclassification. The diagnosis of COPD was based on primary admission diagnosis, and only patients with an admitting diagnosis of asthma were excluded. Patients with coexisting asthma, even if recognised and listed in the 15 secondary diagnosis fields, were not mentioned nor excluded. The inclusion of patients with features of asthma would result in an overestimation of a treatment effect (confounding by indication).

Another potential limitation is the measurement of exposure to the drug of interest. Exposure for the 3 yrs of follow-up was estimated from the first two prescriptions of inhaled corticosteroids following the index hospitalisation. This manner of imputing a daily dose of inhaled corticosteroids over a long period of time has never been validated, and it seems highly likely that patients in real life may change their use of a drug over such a prolonged period of time. In a recent similar database study in patients of ≥ 65 yrs of age with COPD, about half the patients discontinued their inhaled corticosteroids within a year [12]. This leads to the question of biological plausibility: how reasonable is it to expect a reduction in all-cause

mortality of 25% over a 3-yr period based on measured exposure to inhaled steroids for a few months? The biological plausibility is even more questionable because of the finding that patients who received only one dispenser of inhaled corticosteroids during the whole follow-up period (indeterminate doses group) had a 12% reduction in mortality that was almost statistically significant (RR: 0.88; 95% CI: 0.76–1.03). Furthermore, it is still uncertain whether inhaled corticosteroids suppress airway inflammation in COPD. This contrasts with the well-documented and consistent results of a benefit in patients with asthma.

As a clinician it may be tempting to incorporate these findings into clinical practice, in the hope that inhaled corticosteroids will reduce the long-term mortality of COPD patients. However, in contrast to the beneficial effects shown in these observational studies [8–10] in a recent meta-analysis [7], including nine randomised trials of which five assessed mortality as an outcome, the authors were not able to demonstrate any significant effect of regular use of inhaled corticosteroids on all-cause mortality (RR: 0.84; 95% CI: 0.60–1.18). The doses of inhaled corticosteroids were generally similar and almost uniformly high. These studies also have their limitations, considering that they were not originally designed to assess the effect of inhaled corticosteroids on mortality in COPD patients.

Based on the available data, it cannot be concluded that the use of inhaled corticosteroids reduces mortality in patients with chronic obstructive pulmonary disease. It is too early to recommend long-term use of inhaled corticosteroids in chronic obstructive pulmonary disease patients other than for those who have symptomatic disease and repeated exacerbations requiring treatment with antibiotics and oral corticosteroids. This treatment should only be considered after other treatment modalities have been optimised in the patient, including the use of inhaled bronchodilators. There is a need for large randomised clinical trials in appropriate populations of patients with chronic obstructive pulmonary disease. Hopefully, major studies such as the TORCH study will help to clarify this important issue. It is also vital that progress is made in understanding the mechanisms responsible for inflammatory response in chronic obstructive pulmonary disease and what treatments are effective in suppressing inflammation.

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