

PostScript

LETTERS TO THE EDITOR

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Inhaled corticosteroids and mortality in COPD

We read with interest the recent paper by Sin and colleagues¹ which, we believe, raises more questions than it answers.

A major concern is the fact that ascertainment of mortality was incomplete for a significant proportion of patients (973/5086), corresponding to 19% of the total (not the reported 12%) who withdrew prematurely from the study. This loss to follow up was more likely to occur in the placebo group. The authors use the ISOLDE study² to claim that patients who withdrew prematurely were more likely to die, and that therefore the hazard ratio is in fact an underestimate of the benefit of inhaled corticosteroids (ICS). However, the ISOLDE data are themselves contradictory on this point. The claim is based on an abstract from the ISOLDE study that states that 29 deaths occurred before withdrawal and 74 subsequently.³ On the other hand, the original ISOLDE article reported 68 deaths before withdrawal, which would leave only 35 afterwards.² The claim of a higher death rate after withdrawal may therefore be incorrect.

We believe that differential identification of deaths may have occurred as suggested by figure 1 in the paper, and that this could easily have biased the hazard ratio. The figure first implies a hazard ratio of 1 (with no difference in mortality between the ICS and placebo group) during the first 9 months of follow up, the only time period in which every single patient is included and loss to follow up is of no consequence. This initial 9 month period thus involves all 5086 patients and around 50 deaths, a quarter of all deaths. The subsequent apparent benefit of ICS is exclusively the result of spurts of excess mortality in the placebo group that occurred at unusually specific time points—namely, between the 9th and 12th months of follow up and just after the 24th month. In contrast, the rate of mortality in the ICS group appears to be fairly constant at roughly 1.6 deaths per 100 per year throughout the 3 year follow up period. From the natural history of COPD, however, we would also expect a constant rate of mortality in the placebo group—albeit at a higher rate—if ICS

are indeed beneficial. This observation of spurts of excess mortality in the placebo group at specific time points is more suggestive of a study design effect than of a real drug effect. Indeed, if ICS were effective, their benefit is more likely to be gradual throughout the follow up period rather than kicking in to prevent short spurts in mortality precisely at 9 and 24 months after initiation. This phenomenon suggests differential misclassification of deaths or informative censoring between the placebo and ICS groups. The authors could describe the 20 or so deaths, as well as the withdrawals, occurring in the placebo group between the 9th and 12th months of follow up, and after the 24th month.

The reduction in all-cause mortality resulted from a reduction of deaths due to cancer and to other causes, but not a reduction in cardiac deaths, and is therefore not consistent with the mechanism of benefit of ICS in reducing overall mortality which is usually postulated.⁴ Some of the apparent beneficial effect of ICS might be the result of withdrawal of these medications⁵ which will occur in the placebo arm of the trials included in the ISEEC study. Such withdrawal might result in relative adrenal insufficiency. It would therefore be useful to stratify the analysis of the possible benefit of ICS in reducing mortality by prior use of corticosteroids, both inhaled and systemic. Such a stratified analysis should also be considered in the much anticipated TORCH study.

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Inhaled corticosteroids and mortality in COPD: are we there yet?

A broader indication for inhaled corticosteroids (ICS) in COPD has been sought for some time. The recent meta-analysis by Sin *et al*¹ suggesting protection against all-cause mortality is therefore of some interest. Although

not universally confirmed,^{2,3} this tantalising concept is being prospectively evaluated in a 3 year study of high dose ICS (fluticasone propionate 500 µg twice daily, alone or in combination with a long acting β agonist) in COPD patients with forced expiratory volume in 1 second (FEV₁) <60%.⁴

But how might this protection be afforded? Local effects may teleologically provide organ specific protection, potentially reflected by reduced frequency or severity of pulmonary exacerbations. However, COPD is recognised as a systemic inflammatory condition associated with raised systemic inflammatory markers such as C-reactive protein, and this marker is increasingly recognised as an independent risk factor for cardiac mortality.⁵

Important questions revolving around the determinants of all-cause mortality, both generally and in COPD, remain unresolved. How, for instance, should we interpret a positive trial outcome without comparative data regarding the relative impacts of the modification of such risk factors as smoking cessation, diet, exercise, and weight reduction? Secondly, if the benefits provided by corticosteroids could be largely attributed to systemic anti-inflammatory activity, then systemic corticosteroid dosing may be more efficient and potentially cheaper. Finally, these questions will be further complicated by uncertainties regarding dosing, the need for concomitant long acting β agonists, and adverse effect thresholds.

Currently recommended indications for ICS in COPD include the prevention of exacerbations in those with FEV₁ <50% and "the prevention of decline in health status".^{6,7} Clarification and the beneficial extension of these indications would be welcomed.

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