Inhaled corticosteroids and mortality in COPD

We read with interest the recent paper by Sin and colleagues’ 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 (973/1086), corresponding to 19% of the total (not the reported 12%) who withdrew prematurely from the study. This loss to follow-up is of no consequence. This initial withdrawal, which would leave only 35% after 24 months, is easily explained by the severity of illness and the difficulty in continuing treatment. But how might this protection be afforded? One possibility is that the benefits provided by corticosteroids could be largely attributed to systemic anti-inflammatory activity, then 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 death in ‘fairly’ severe status”1. Clarification and the beneficial extension of these indications would be welcomed.

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References

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 systematic review by Sin et al.1 suggesting protection against all-cause mortality is therefore of some interest. Although not universally confirmed,2 this tantalising concept is being prospectively evaluated in a 3 year study of high dose ICS (fluticasone propionate 500 µg twice daily or a combination with a long acting β agonist) in COPD patients with forced expiratory volume in 1 second (FEV1) <60%.3

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 markers such as C-reactive protein, and this marker is increasingly recognised as an independent risk factor for cardiac mortality.4

Important questions revolving around the differential identification of all-causes of death 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 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 death in ‘fairly’ severe status”5. Clarification and the beneficial extension of these indications would be welcomed.

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References