PostScript

LETTERS TO THE EDITOR

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Inhaled corticosteroids and mortality in COPD

In response to the letter by Ernst and Suissa[1] published in the August edition of *Thorax*, the issue of incomplete ascertainment of vital status information in five of the seven trials included in the pooled analysis was discussed in the paper.[2] This would only make a meaningful impact on the overall results if patients in the inhaled corticosteroid group who withdrew were more likely to die than those patients who withdrew from the placebo arm of the trials. There is no material reason to believe that this would be the case. In the five trials with incomplete data on mortality, inhaled corticosteroids were effective in reducing all-cause mortality in patients with a forced expiratory volume in 1 second (FEV_1) of <60% of predicted (adjusted hazards ratio 0.69). In the two trials for which complete mortality data were available (ISOLDE and LHS-2), inhaled corticosteroids were just as effective in reducing mortality (adjusted hazard ratio 0.60), providing assurances that incomplete follow up data did not bias the overall findings.[2]

The seven trials largely recruited patients who had stable COPD and were free of life threatening co-morbidities at baseline because the end points of these studies were not mortality but were exacerbations or lung function. Not surprisingly, the overall mortality rate in the first 6–9 months was very low. However, with passage of time the mortality rate in the placebo arm increased, as would be expected given the natural history of COPD.[3] In contrast, the mortality rate remained consistently low in the group that received inhaled corticosteroids, indicating a (protective) survival effect of these medications in COPD.

As pointed out in the paper, the cause-specific mortality data should be interpreted cautiously.[2] We relied on death certificates and/or monitoring reports to ascribe specific causes of deaths. However, in patients with COPD, such data may not be reliable.[4]

While we agree with Drs Ernst and Suissa[1] that inhaled corticosteroids may have salutary effects on the cardiovascular system, causation has not been fully established. There are some emerging data on the potential effects of inhaled corticosteroids on oncogenesis that should not be dismissed.[5 6] We agree with Drs Ernst and Suissa that our paper ''raises more questions than it answers''. We hope that these questions stimulate more research in COPD which, in time, we believe will lead to novel discoveries of mechanisms and therapeutic compounds that will improve the health and health outcomes of patients with COPD across the world.

D D Sin
for the ISEEC Steering Committee

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Inhaled corticosteroids and mortality in COPD

In his letter published in the August edition of *Thorax*, Dr Stirling[1] raises many issues regarding the role of inhaled corticosteroids in chronic obstructive pulmonary disease (COPD). As pointed out by Dr Stirling, there are compelling data to indicate that inhaled corticosteroids reduce clinically relevant exacerbations by nearly a third and improve health status and quality of life for patients with COPD.[2 3] They also reduce emergency visits and hospital admissions.[4] Our pooled analysis extends these findings by demonstrating a salutary effect on mortality.[5] The precise mechanism(s) by which these effects occur are uncertain.

COPD is an inflammatory disorder which is characterised by both local lung and systemic inflammation[6 7] and the intensity of the inflammatory process relates to COPD progression.[8] Inhaled corticosteroids appear to attenuate lung and systemic inflammation.[9–11] However, inhaled corticosteroids have pleotropic effects and some of these effects—such as restoring β_2 adrenoceptor sensitivity and reducing oxidant load in the airways—may be of relevance in COPD.[12] As such, it would be premature and presumptuous to attribute the clinical benefits exclusively to their anti-inflammatory properties. While oral corticosteroids are more powerful anti-inflammatory agents than are inhaled corticosteroids, they are also fraught with many side effects.[13] Accordingly, they cannot be recommended for long term use in most patients.

We agree with Dr Stirling that there are other effective interventions in COPD—including smoking cessation, pulmonary rehabilitation, and co-morbidity management—that deserve attention.[14] Inhaled corticosteroids should not replace any of these effective interventions; rather, they should be regarded as complementary therapies in the management of COPD.

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