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 (973/5086), corresponding to 19% of the total (not just 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 study 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. This claim is based on an abstract of the ISOLDE study that states that 29 deaths occurred before withdrawal and 74 subsequently. On the other hand, the original ISOLDE article reported 68 deaths before withdrawal, which would leave only 35 afterwards. 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 treatment. 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. Some of the apparent beneficial effect of ICS might be the result of withdrawal of these medications which will occur in the placebo arm of the trials included in the ISEE study. Such withdrawal might result in reduced anti-inflammatory sufficiency. 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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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 reasoning is that mortality in COPD is exclusively the result of spurs of excess mortality in the placebo group—albeit at a higher rate—if ICS are indeed beneficial. This observation of spurs of excess mortality in the placebo group at specific time points is more suggestive of a short time 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 spurs 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.

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