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LETTER

Reply to: "Intraclass Difference in Pneumonia Risk with Fluticasone and Budesonide in COPD: A Systematic Review of Evidence from Direct-Comparison Studies" [Letter]

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Dear editor

We read with interest the article by Lodise et al.[1] The analysis is fundamentally flawed. The authors conclude that there is a greater risk of pneumonia with fluticasone compared with budesonide (BUD). There is no such drug as fluticasone; there is fluticasone propionate (FP) and fluticasone furoate (FF). These are different compounds with different molecular structures, potency and dosages. Of the six fluticasone studies discussed,[1] five investigated FP, whereas one (Lipson et al) investigated FF. These drugs need to be analysed separately.

A major problem with analyses that compare pneumonia rates is that multiple risk factors for ICS-related pneumonia exist.[2] Such analyses require valid comparison groups, which can only be done reliably by comparing pneumonia rates between ICS- and non-ICS-containing treatments within the same trial. This was done in a systematic review[3] not cited by Lodise et al. It showed no difference between fluticasone- versus BUD-containing treatments with regards to serious or fatal pneumonia events; there was a significantly higher risk of any pneumonia event with fluticasone-containing treatments but the authors advised caution due to differences in pneumonia assessment between studies and the lack of head-to-head trials.[3]

Unfortunately, there are few direct comparisons between FF and BUD. Lodise et al do quote Lipson et al but only partially. At 24 weeks there was a higher rate of pneumonia with FF/umeclidinium/vilanterol (FF/UMEC/VI) compared with BUD/formoterol (BUD/FOR), but at 52 weeks there was no difference, which the authors fail to mention.[1]

When Lodise et al was published they will have been aware of the results of the ETHOS study.[4] The ETHOS and IMPACT studies recruited similar groups of patients with symptomatic COPD and a history of exacerbations, but defined pneumonia in different ways, which may result in different absolute pneumonia rates.[4,5] A within-study comparison of pneumonia events shows very similar pneumonia rate ratios between triple therapy and non-ICS-containing treatments (1.7 in ETHOS for BUD 320µg/glycopyrronium [GLY]/FOR vs GLY/FOR; 1.6 in IMPACT for FF/UMEC/VI vs UMEC/VI).[4,5]

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The other studies referenced are observational, and the increased pneumonia risk identified in this systematic review is highly dependent on the PATHOS study by Janson et al. This was an observational study in Sweden for which Lodise et al[1] failed to adequately identify and assess risk of bias, an essential element of systematic literature reviews. Propensity matching was used in an attempt to balance patients using the two ICS/LABA treatments in PATHOS, but this did not include factors known to be important risk predictors for ICS-related pneumonia in COPD.[2,6] Lung function data were included where available in the propensity score, but it is unclear how many patients had missing data. Contemporaneous data suggest that spirometry is only conducted in 45–52% of patients with COPD in primary care in Sweden,[7,8] suggesting that many patients in PATHOS may have lung function unaccounted for. Janson et al was a secondary analysis of a study whose stated primary aim was to describe the evolution of COPD management in Sweden over an 11-year period.[9] Unusually, the pneumonia analysis was published before the paper describing the protocol and primary purpose of the study meaning that referees and readers of the pneumonia analysis could not fully understand the potential biases. The primary study results showed significant improvements in outcomes in Sweden over the 11-year period and a follow-up paper showed that clinics with a trained respiratory nurse had better outcomes than those that did not,[9,10] but neither the index date nor these differences were accounted for in propensity matching in the PATHOS pneumonia analysis. Lastly, and perhaps most importantly, although death due to pneumonia was more common in the patients prescribed FP by their physicians, overall mortality was the same, implying that there were more deaths from other causes with BUD compared with FP, this is not discussed.

Finally the European Medicines Agency, an independent body with a responsibility for patient safety, has twice examined whether there is any difference in pneumonia rates between different ICSs and concluded that there is no intraclass difference.[11]

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