

The Therapeutic Index as Indicated by Efficacy/Safety Ratio May Be Primarily Assessed by Meta-Analysis of the Efficacy of ICS Combination Therapy for COPD [Letter]

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Dear editor

With interest, we read the review article by Ding et al¹ published in the recent issue of the *International Journal of Chronic Obstructive Pulmonary Disease* (COPD). They performed a systematic literature review and meta-analysis of randomized clinical trials (RCTs) comparing the effect of inhaled corticosteroid (ICS)-containing combination therapy and non-ICS regimen in patients with COPD. The authors have found that a wide range of patients with COPD could benefit from dual and triple ICS-containing therapy. In addition to the significant reduction of acute exacerbation by ICS-containing therapy, a significant improvement in lung function was observed for ICS/long-acting β_2 agonists (LABA) versus LABA and ICS/LABA/long-acting anti-muscarinic agents (LAMA) versus LAMA regimens. A significant improvement in quality of life (QoL) was also observed with ICS versus non-ICS therapy. However, the treatment-emergent adverse events were not fully demonstrated. The increased risk of pneumonia following inhaled steroids and ICS-containing combination therapy for COPD is concerning.² The other recent meta-analysis revealed that ICS-containing triple therapy resulted in 230 fewer AECOPDs but 16 more cases of pneumonia per 1000 patients.³ In Japanese population data, a significant increase in pneumonia events with ICS/LAMA/LABA treatment compared to with LAMA/LABA treatment has also been reported (OR, 3.38; 95% CI, 1.58 to 7.22; $P = 0.002$; $I^2 = 0\%$).⁴ This safety issue of ICS-containing triple therapy is very important for treatment decisions in COPD and should be summarized in the abstract of the current review paper. Although there are some discussions about the pneumonia risk issue in the body of the text, no data is available in the results section of their abstract.

Importantly, we should consider the inhaled steroids associated pneumonia risk in COPD with caution.⁵ Although severe pneumonia would result in the significant increase of mortality in COPD, most of the community acquired pneumonia (CAP) and nursing- and healthcare-associated pneumonia (NHAP) in chronic respiratory diseases could be well treated with appropriate selection of antibiotics and comprehensive therapy including systemic administration of steroids.⁶ Therefore, we consider the therapeutic merit of the reduced effect on exacerbation in combination with the possible mortality risk of ICS-related pneumonia. The therapeutic index as indicated by efficacy/safety ratio may be primarily assessed by the meta-analysis of the efficacy of ICS combination therapy for COPD. A high therapeutic index is preferable for an ICS combination drug to have a favorable safety and efficacy profile.

Disclosure

The author reports no conflicts of interest in this communication.

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