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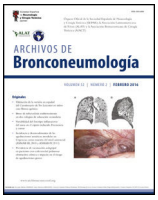

Editorial

Inhaled Corticosteroids and Lung Cancer in COPD☆

Corticosteroides inhalados y cáncer de pulmón en la EPOC

Luis M. Seijo,[a,b] Germán Peces-Barba[b,c,*]

[a] *Clínica Universidad de Navarra, Madrid, Spain*
[b] *Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES), Instituto de Salud Carlos III, Madrid, Spain*
[c] *Hospital Fundación Jiménez Díaz, Madrid, Spain*

Lung cancer (LC) is epidemiologically linked with morphological alterations typical of emphysema and with lung function changes observed in COPD, mainly due to exposure to tobacco smoke and pollution. The reasons for these associations have been widely debated, and the presence of shared susceptibility genes, alterations in DNA repair, and chronic inflammation have all been considered.[1] However, LC is not only more frequent in COPD patients, it is also more aggressive and associated with a worse prognosis.[2] For this reason, there is an urgent need to identify strategies for early detection, treatment, and personalized chemoprevention in this special risk group.

The association between inflammation, COPD, and LC has only been partially described. The expression of transcription factor NF-κβ, for example, increases with smoking and plays a role in the pathogenesis of COPD. This inflammatory mediator has also been associated with carcinogenesis and muscle mass loss.[1] Other inflammatory mediators associated with both COPD and LC include the signaling pathways of phosphatidylinositol-3-kinase and Wnts proteins (contraction of Wintgless gene and Int-1 gene), the aberrant expression of epidermal growth factor receptor, and the epithelial–mesenchymal transition.[1] In this context, it is not surprising to find anti-inflammatory strategies used as potential initiatives for preventing LC in COPD patients. Of special relevance is the proposal for the use of inhaled corticosteroids (ICS), since this is a treatment indicated in some COPD patients that potentially combines an anti-inflammatory effect with a chemopreventive effect.

Evidence in favor of corticosteroids in the prevention of LC is emerging from both experimental animal studies and observational studies in humans. Dexamethasone inhibits carcinogenesis in various animal models of LC and is especially effective in combination with myoinositol.[3] Inhaled budesonide has also demonstrated efficacy as a chemopreventive agent in various animal models.[4] Considerable evidence is available in humans, but it should be pointed out that the benefit of these drugs has not been confirmed in sufficiently large clinical trials, although benefits have been reported by some authors.[5] A substudy of the COSMOS screening trial randomized 200 patients to receive budesonide or placebo for a year with a subsequent follow-up of 5 years.[6] Treatment with budesonide was associated with a decrease in the size of non-solid or partially solid nodules detected by CT, but no reduction was observed in the appearance of new nodules or cancerous lesions compared to placebo. Another analysis of several studies that investigated the use of ICS in COPD, showed that these drugs decreased all-cause mortality and demonstrated a declining trend in deaths from cancer.[7] A recent observational study carried out on large healthcare databases has identified this same relationship.[8] The effect appears to be dose-dependent, as it is more intense when higher doses of ICS are administered.[9] The preventive effect also appears to be more marked in women and in former smokers.[10] Although the evidence comes from studies with large methodological differences and a wide geographical distribution, ICSs reduce the probability of developing LC by around 60%. This reproducibility of the effect of steroids is intriguing and contributes to its biological plausibility. In contrast to the above-mentioned studies, the disappointing outcomes of ICS in some prospective studies of patients with bronchial dysplasia should be noted. Inhaled fluticasone did not influence the natural disease course of premalignant lesions of the airway in 108 patients with a history of laryngeal carcinoma or lung cancer.[11] Short-term courses of high-dose budesonide also failed to show any benefit in a study of 112 patients with bronchial dysplasia.[12]

The relationship between ICS, inflammation, and COPD has been studied in much more depth, but it still remains unclear. It is recognized that ICS reduce inflammation of the airways, mainly when administered in combination with betamimetic bronchodilators. In addition to their effect on eosinophils, levels of T lymphocytes, neutrophils and other biomarkers levels also decrease, but we cannot be sure that these changes are behind the clinical effect detected. Nor do we have information on their effect in mild cases of COPD, omitted in these studies. We need a better understanding of the effect of ICS on inflammation in COPD, an effect which is not limited to the lung, but also includes the bone marrow, pulmonary circulation, and the epithelial–mesenchymal transition. We also need

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* Corresponding author.
E-mail address: GPeces@fjd.es (G. Peces-Barba).

to determine their potential effect on mild and moderate cases of COPD and on the different phenotypes and endotypes of the disease.

ICS are not free of side effects, especially in the long term, and they have been associated with the onset of diabetes and osteoporosis.[13,14] In addition, larger clinical trials, such as UPLIFT, associated their use with a higher incidence of pneumonia.[15] Despite the side effects, we believe that COPD patients treated with ICS may possibly experience a reduction in the risk of LC. The evidence in favor is weak because it is gleaned from observational epidemiological studies, and unfortunately clinical trials conducted to date have not had sufficient statistical power or a long enough follow-up to corroborate these findings. A good approach might be a comprehensive analysis of all patients included in clinical trials conducted with ICS. Nevertheless, since we are dealing here with a very prevalent cancer with high morbidity and mortality, we believe that to achieve a definitive answer we would need a carefully designed clinical trial with longitudinal follow-up to definitively analyze the impact of ICS on reducing the risk of LC in patients with COPD.

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