



Diagnosis of asthma–COPD overlap: the five commandments

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Asthma–COPD overlap is different from COPD and from obstructive asthma in never-smokers
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There is wide consensus regarding the excessive use of inhaled corticosteroids (ICS) in chronic obstructive pulmonary disease (COPD) [1, 2]. The approved indication for ICS in COPD is the treatment of patients with impaired lung function (usually forced expiratory volume in 1 s (FEV₁) <60% predicted) and frequent exacerbations, but the recent Global Initiative for Chronic Obstructive Lung Disease (GOLD) strategic document indicates that even in these cases, dual bronchodilation should be preferred to the use of a combination containing ICS. However, long-acting β_2 -agonists/ICS may be the first choice of treatment in patients with a history and/or findings suggestive of asthma–COPD overlap (ACO) and/or high blood eosinophil counts [3]. Therefore, the history and/or findings of ACO are crucial for the therapeutic decision to prescribe an ICS or not in COPD but no clear indication is provided about what history and/or findings of ACO mean [3], and this has been highlighted as one of the limitations of the new proposal for pharmacological treatment [4]. In addition, the same document indicates that regular treatment with ICS increases the risk of pneumonia [3]. Therefore, the clinician must evaluate the risk/benefit ratio in each patient before the prescription of an ICS, and the diagnosis of ACO plays a fundamental role in this evaluation. In contrast, the diagnosis of ACO does not have significant therapeutic implications in asthma because the initial therapy is not different between pure asthmatics and overlap patients.

GOLD and the Global Initiative for Asthma define ACO as persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD, and indicate that ACO includes different clinical phenotypes and there are likely to be several different underlying mechanisms [5]. This approach to the definition is imprecise because it does not indicate how many of the features are necessary and/or whether they have the same relevance for the diagnosis of ACO. An example is the presence of significant exposure to tobacco smoke as one of the features favouring COPD. However, smoking (or exposure to biomass fuels) should be a necessary factor for the diagnosis of ACO; a never-smoking asthmatic with persistent airflow obstruction cannot be diagnosed with ACO. In this case, the diagnosis should be obstructive asthma but no overlap with COPD can be postulated if there is no significant exposure to inhaled risk factors. A completely different situation is an asthmatic who smokes, because smoking asthmatics are at increased risk of developing chronic airflow limitation, particularly in subjects with asthma onset after 10 years of age [6]. However, the chronic airflow limitation developed in smoking asthmatics has some particular characteristics that are different from those of COPD in individuals who have never had asthma. In smoking asthmatics with chronic airflow limitation, bronchial

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hyperresponsiveness, wheezing and allergic rhinitis are more frequent, and they have greater IgE sensitisation and higher plasma levels of total IgE compared with COPD developed in nonasthmatic smokers [7]. Among the 25% of COPD patients in the ECLIPSE cohort considered to have ACO because of a previous diagnosis of asthma, 88% also reported wheezing, 72% a current diagnosis of asthma, 27% atopy, and 26% both atopy and wheezing [8]. These “asthmatic smokers with COPD” fulfil the profile of patients with ACO [9].

Patients with ACO are clearly different from nonsmoking asthmatics. In this issue of the *European Respiratory Journal*, TOMMOLA *et al.* [10] present the results of an investigation in 188 patients with adult-onset asthma 12 years after diagnosis, and compare the characteristics of never- and ex-smokers with <10 pack-years (obstructive asthma), nonobstructive patients with ≥ 10 pack-years, and ACO patients with ≥ 10 pack-years and FEV₁/forced vital capacity <0.7. As expected, there were no differences in clinical markers of type 2 immune responses (Th2) (frequency of rhinitis, atopy and allergy) but patients with ACO had worse diffusion capacity, more neutrophils and higher concentrations of interleukin (IL)-6, characteristics that are usually associated with COPD. Of great interest is the comparison between patients with obstructive asthma or ACO. Although the number of patients in both groups was small, individuals with ACO again had significantly reduced diffusion capacity, and significantly higher concentrations of neutrophils and IL-6, while blood eosinophils, IgE and exhaled nitric oxide fraction (FeNO) were similar between groups. These differences reflect the impact of cigarette smoking in adult asthmatics with the change in their inflammatory characteristics.

Another recent study has shown that obstructive smoking asthmatics (or ACO) had an older age at diagnosis compared with obstructive asthmatics (48 *versus* 35 years), and worse airflow obstruction and diffusion capacity compared with nonsmoking obstructive asthmatics [11]. These differences can also be observed by computed tomography, which shows distinct characteristics of ACO compared to obstructive asthma or COPD [12, 13]. Patients with ACO present a higher emphysema index and a greater upper zone predominant distribution of emphysema, compared with obstructive asthma [14]. These differences indicate that asthmatics with significant exposure to smoking develop a different type of chronic obstructive airflow disease (COAD) with mixed characteristics of asthma and COPD, and justify the use of the term ACO.

But ACO can also be diagnosed in patients without diagnostic criteria for asthma. There are smokers who develop chronic airflow limitation in a background of eosinophilic inflammation, even without the diagnosis of previous or current asthma. CHRISTENSON *et al.* [15] developed a type 2 signature (T2S) genetic score that correlated well with Th2-associated clinical characteristics in asthmatic patients and found that approximately 20% of COPD patients had increased T2S expression. They also observed that the T2S in COPD was associated with increased tissue eosinophil numbers, increased blood eosinophils, increased bronchodilator responsiveness and a greater response to ICS [15]. This study suggests that the T2S may serve as a biomarker to identify ACO patients who will benefit from ICS treatment. Interestingly, a very recent study has also suggested that the Th2 endotype could be used to identify patients with COPD that may respond to ICS better than the clinical characteristics associated with ACO [11].

The most accessible marker of the Th2 type of inflammation is increased concentrations of blood eosinophils, and consistently, blood and sputum eosinophil counts are significantly higher in patients with ACO compared with COPD [16]. The increase in blood eosinophils in COPD has been associated with increased reversibility of airflow obstruction [15–17], with higher FeNO [18, 19], and a better response to ICS in terms of improvements in lung function [15, 20], prevention of exacerbations [21] and reducing the rate of decline in lung function [22]. Despite the growing evidence for the value of blood eosinophil counts as a marker of ICS response in COPD, there are no prospective *ad hoc* studies designed with this specific aim and there is no general agreement yet on a threshold to define high blood eosinophil counts.

The most recently published consensus of ACO included six criteria, three of which are major (persistent airflow limitation, tobacco smoking and previous asthma or reversibility >400 mL FEV₁) and three minor (history of atopy or rhinitis, at least two positive bronchodilator tests and ≥ 300 blood eosinophils per μL) [23]. In an attempt to simplify this, the Spanish guidelines for COPD and for asthma agreed on a definition of ACO that included patients with a concomitant diagnosis of both diseases or patients with COPD and either ≥ 300 blood eosinophils per μL or a reversibility >400 mL or both [24]. The criterion of high reversibility is less important in clinical practice because it is very infrequent. In the ECLIPSE and ISOLDE trials, only ~5% of patients showed reversibility >400 mL [25, 26] and probably most of these patients had some degree of eosinophilic inflammation as well [15–17].

These criteria may classify different types of patients as having ACO [27, 28] but all of them have the common denominator of an enhanced response to ICS. They are only intended to be a guide for nonspecialist clinicians but it is clear that the diagnostic approach to COAD is more complex, and it is not

possible to classify all patients into a limited number of categories. However, it is important to provide a few clear and basic ideas: the five commandments of ACO diagnosis.

- 1) A patient with asthma may develop non-fully reversible airflow obstruction but this is not COPD, not even ACO; it is obstructive asthma.
- 2) A patient with asthma who smokes may also develop non-fully reversible airflow obstruction, which differs from obstructive asthma and from “pure” COPD. This is the most frequent type of patient with ACO.
- 3) Some patients who smoke and develop COPD may have a genetic Th2 background (even in the absence of a previous history of asthma) and can be identified by high eosinophil counts in peripheral blood. These individuals could be included under the umbrella term of ACO.
- 4) A patient with COPD and a positive bronchodilator test (>200 mL and >12% FEV₁ change) has reversible COPD but is not an asthmatic, or even ACO.
- 5) A patient with COPD and a very positive bronchodilator test (>400 mL FEV₁ change) is more likely to have some features of asthma and could also be classified as ACO.

Obviously, these statements are only “opinion based”, as this is an editorial and not a guideline, but they are supported by a large body of evidence. Nevertheless, if future prospective studies confirm the predictive value of eosinophils for response to ICS in COPD and identify a valid cut-off, clinicians will no longer need ACO and it will be replaced by eosinophilic or Th2 COPD. Some authors have already postulated the extinction of ACO and the identification of endotypes in COAD that will allow a personalised approach to therapy [11, 29] but in the meantime, a clear and simple (although not perfect) definition of ACO should help to improve the management of patients with COAD.

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