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EDITORIAL

Asthma-chronic obstructive pulmonary disease overlap syndrome: A diagnostic puzzle for the clinicians

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Abstract

Although asthma and chronic obstructive pulmonary disease (COPD) are distinct airway diseases characterized by chronic inflammation, in some cases distinguishing between them is puzzling. For example, chronic smoking leads asthmatic inflammation to a differentiated pattern resembling the COPD inflammation, and in some cases to fixed obstruction as in COPD, and on the other hand, few COPD patients may present with airway reversibility. ACOS is the condition sharing features encountered both in asthma and COPD. Asthma-COPD overlap syndrome (ACOS) represents a diagnostic challenge in the clinical practice, since there is lack of specific indicators to distinguish it from asthma or COPD, and moreover, genetic risk factors, underlying pathology and molecular pathways, clinical characteristics, therapeutic interventions, response to treatment and prognosis are poorly described. The management of ACOS is recommended to be individualized and should target on the maximum effectiveness with the least side effects. Combination therapy with ICS/LABA or LAMA, or newly developed specific anti-eosinophil therapies and treatments specifically targeting neutrophils might be of relevance in the management of ACOS, but studies are needed in order to assess the response and prognosis. Based on the current knowledge about ACOS thus far, it would be recommended that we approached chronic obstructive airway disease rather by describing than by classifying the disease; this would allow us to have a picture that better describes the disease and to implement an individualized therapeutic approach, according to the custom phenotype. Nevertheless, more studies are needed in order to clarify several important issues with regard to ACOS, such as the genetic risk factors for developing ACOS, the links between genotype and phenotype, the molecular pathways and underlying mechanisms of ACOS, the identification of possible specific biomarkers for diagnosis and targeted treatment, the optimal therapeutic interventions, and finally, the prognosis of ACOS.

Key words: Asthma; Chronic obstructive pulmonary disease; Asthma-chronic obstructive pulmonary disease overlap syndrome; Diagnostic challenges; Therapeutic dilemmas

Core tip: Asthma-chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS) represents a diagnostic challenge in the clinical practice, since there is lack of specific indicators to distinguish it from asthma or COPD, and moreover, genetic risk factors, underlying pathology and molecular pathways, clinical characteristics, therapeutic interventions, response to treatment and prognosis are poorly described. Combination therapy with ICS/LABA or LAMA, or newly developed specific anti-eosinophil therapies and treatments specifically targeting neutrophils might be of relevance in the management of ACOS. More studies are needed in order to clarify the underlying mechanisms, the clinical aspects and the prognosis of ACOS.

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Chronic obstructive pulmonary disease (COPD) and asthma are the commonest chronic airway diseases both characterized by chronic inflammation. Although sharing this common characteristic they are quite different diseases in terms of the anatomic sites involved, the pathologic changes and the pattern of inflammation[1]. It's well established that chronic smoking leads asthmatic inflammation to a differentiated pattern resembling the COPD inflammation, often making the differentiation between these two diseases puzzling[2]. It has repeatedly been shown that patients who have been previously diagnosed with COPD can have features of asthma, and patients with asthma may develop persistent airflow limitation similar to COPD. On this ground, in 2015, Global Initiative for Asthma and Global Initiative for Chronic Obstructive Lung Disease provided a clinical description of asthma-COPD overlap syndrome (ACOS) with the following description: "ACOS is characterized by persistent airflow limitation with several features usually associated with asthma and several features usually associated with COPD. ACOS is therefore identified by the features that it shares with both asthma and COPD"[2].

Up to date, many studies have been performed in order to establish prevalence, risk factors, comorbidities and factors that determine disease progression in patients who could be referred to as having ACOS. It has been shown that patients with ACOS usually present with a distinct clinical manifestation characterized by increased airflow reversibility, more exacerbations and more severe symptoms (dyspnea), have more frequent adverse outcomes than those with asthma or COPD alone, and utilize a large proportion of medical resources[3]. Identifying patients with ACOS seems therefore relevant for the management of their disease[4,5].

However, for the moment, ACOS represents a diagnostic challenge in the clinical practice, since there is lack of specific indicators to distinguish it from asthma or COPD, and moreover, genetic risk factors, underlying pathology and molecular pathways, clinical characteristics, therapeutic interventions, response to treatment and prognosis are poorly described. The management of ACOS is recommended to be individualized aiming to the optimum effectiveness with the least side effects. However, a serious obstacle occurs during the diagnostic approach which depends on the origin of patient population. The following clinical populations pose the greatest ACOS diagnostic challenges: Asthma patients who have developed strict obstruction with no reversibility and COPD patients with reversible airway limitation and features of asthma. The identification of specific biomarkers for ACOS would facilitate its differentiation from asthma or COPD[3]. In the absence of a single technique or a specific marker to establish the diagnosis and in the lack of specific symptoms for the disease, the diagnosis of ACOS is based upon criteria, which of course are not definitive[2]. Therefore, in several occasions the diagnosis of ACOS is often modified after an initial therapeutic trial.

The diversities in diagnosing ACOS are reflected on the estimations of its prevalence. In the PLATINO study, the prevalence of ACOS in the general population has been estimated as 1.8%, based on symptoms and pulmonary function tests[4], whereas in the United States population it was estimated as 2.7% based on physician-diagnosed asthma and COPD or self reported history[5]. When the diagnosis of ACOS referred to patients with a previous history of asthma with concurrent symptoms of chronic bronchitis and/or impairment in the diffusing capacity of the lung for carbon monoxide its prevalence estimated to reach 29%[6]. On the other hand, when the diagnosis of ACOS referred to patients with a previous history of COPD presenting with reversibility or other features of asthma, its prevalence was as high as 55%[7]. It is quiet evident from the above mentioned data, that the prevalence of ACOS depends on the type of patients from which it is originated and the measures used to diagnose it.

The principal goals of managing ACOS do not differ from those in asthma and COPD: Relief and control of symptoms, elimination of exacerbations or reduction of exacerbation rate, improvement and stabilization of lung function and minimal adverse effects from treatment. The global management should also include prophylactic measures in order to optimize patient's prognosis such as smoking cessation, avoidance of irritant agents such as pollutants or allergens, flu vaccination, education, pulmonary rehabilitation and management of comorbidities[8-10]. Patients with ACOS may improve with a combination treatment with ICS/LABA or LAMA[11,12], however, there is limited data on the response to most of the available therapies. Eosinophilic inflammation has not been shown as a constant distinguisher of ACOS compared with COPD and asthma alone, therefore, treatment targeting eosinophils should be reserved for

patients with proven eosinophilic inflammation.

With regard to bronchodilator therapy, thus far, the only placebo-controlled study in ACOS has shown that once daily tiotropium bromide significantly improved FEV_1, peak expiratory flow rates and decreased the need for rescue therapy[13]. So far, no further clinical studies on long-acting anticholinergics or β2 agonists have been performed. However, since reversibility is not constantly different between ACOS and COPD or asthma alone, future studies should focus on reversibility of chronic airflow obstruction and hyperinflation regardless of underlying phenotype. Newly developed specific anti-eosinophil therapies [anti interleukin (IL)-5, IL-13, IL-33 antibodies] and treatments specifically targeting neutrophils (macrolides, cytokine receptor CXCR2 antagonists, phosphodiesterase type 4 inhibitors, p38 mitogen activated protein kinase inhibitors, anti IL-1 and IL-17 antibodies) might be of relevance, especially for patients with ACOS[14,15].

Based on the current knowledge about ACOS thus far, we could assume that ACOS may be a distinct manifestation of a spectrum of chronic obstructive airway diseases, with asthma and COPD at the two ends of the spectrum. Alternatively, in agreement with Tho *et al*[16], we could consent that ACOS is "an interim term" applicable to patients difficult to be distinguished as being asthma or COPD[17]. It would be recommended that we approached chronic obstructive airway disease rather by describing than by classifying the disease[18]; this would allow us to have all the elements that better describe the disease and to implement an individualized therapeutic approach according to the custom phenotype[19].

Nevertheless, more studies are needed in order to clarify several important issues with regard to ACOS: The genetic risk factors predisposing to ACOS, the links between genotype and phenotype, the molecular pathways of ACOS in order to reveal the underlying mechanisms of ACOS, the identification of possible specific biomarkers for diagnosis and targeted treatment, the optimal therapeutic interventions, and finally, the prognosis of ACOS.

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