Original Article

Accuracy of a New Algorithm to Identify Asthma–COPD Overlap (ACO) Patients in a Cohort of Patients with Chronic Obstructive Airway Disease

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ABSTRACT

Objectives: We aimed to characterize the clinical, functional and inflammatory features of patients diagnosed diagnosed with ACO according to a new algorithm and to compare them with those of other chronic obstructive airway disease (COAD) categories (asthma and COPD).

Methods: ACO was diagnosed in a cohort of COAD patients in those patients with COPD who were either diagnosed with current asthma or showed significant blood eosinophilia ($\geq$300 cells/μl) and/or a very positive bronchodilator response (>400 ml and >15% in FEV1).

Results: Eighty-seven (29.8%) out of 292 patients fulfilled the ACO diagnostic criteria (12.8% asthmatics who smoked <20 pack-years, 100% of asthmatics who smoked $\geq$20 pack-years, 47.7% of COPD with >200 eosinophils/μl in blood and none with non-eosinophilic COPD). ACO, asthma and COPD patients showed no differences in symptoms or exacerbation rate. Mean pre-bronchodilator FEV1 in ACO and asthma were similar (1741 vs 1771 ml), higher than in COPD (1431 ml, $p < 0.05$). DLCO was lower in ACO than in asthma (68.1 vs 84.1%) and similar to COPD (64.5%). Mean blood eosinophil count was similar in ACO and asthma (360 vs 305 cells/μl) and higher than in COPD (170 cells/μl). Periostin levels were similar in ACO to COPD (36.6 and 36.5 IU/ml) and lower than in asthma (41.5 IU/ml, $p < 0.05$), whereas FeNO levels in ACO were intermediate.

Conclusion: This algorithm classifies as ACO all smoking asthmatics with non-fully reversible airway obstruction and a considerable proportion of e-COPD patients, highlighting those who can benefit from inhaled corticosteroids.

Precisión de un nuevo algoritmo para identificar pacientes con superposición asma/EPOC (ACO) en una cohorte de pacientes con enfermedad obstructiva crónica

RESUMEN

Objetivos: Nuestro objetivo fue definir las características clínicas, funcionales e inflamatorias de los pacientes diagnosticados con superposición asma/EPOC (ACO, por sus siglas en inglés) según un nuevo algoritmo y compararlas con las de otras categorías de enfermedades obstructivas crónicas de las vías aéreas (COAD, por sus siglas en inglés) como el asma y la EPOC.

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Métodos: En una cohorte de sujetos con COAD, se diagnosticó ACO en aquellos pacientes con EPOC que, además, tenían un diagnóstico actual de asma o que presentaban eosinofilia sanguínea significativa ($\geq$300 células/μl) y/o respuesta muy positiva a broncodilatadores (>400 ml y >15% en FEV_1).

Resultados: Ochenta y siete (29,8%) de 292 pacientes cumplieron con los criterios de diagnóstico de ACO (12,8% de asmáticos que fumaron <20 paquete/año, 100% de asmáticos que fumaron $\geq$20 paquete/año, 47,7% de COPD con >200 eosinófilos/μl en sangre y ninguno con EPOC no eosinofílica). Los pacientes con ACO, asma o EPOC no mostraron diferencias en los síntomas o en la tasa de exacerbación. El FEV_1 promedio prebroncodilatador en pacientes con ACO o asma fue similar (1.741 vs. 1.771 ml), y mayor que en aquellos con EPOC (1.431 ml, p < 0,05). El DLCO fue menor en individuos con ACO que en aquellos con asma (68,1 vs. 84,1%) y similar al de los pacientes con EPOC (64,5%). El recuento promedio de eosinófilos en sangre fue similar en pacientes con ACO o asma (360 vs. 305 células/μl) y mayor que en los de EPOC (170 células/μl). Los niveles de periostina fueron similares en el grupo con ACO o con EPOC (36,6 y 36,5 UI/ml) y menores que en el pacientes con asma (41,5 UI/ml, p < 0,05), mientras que los niveles de FeNO en el grupo ACO fueron intermedios.

Conclusión: Este algoritmo clasifica como ACO a todos los fumadores asmáticos con obstrucción no reversible de las vías respiratorias y una proporción considerable de pacientes con EPOC eosinofílica, destacando aquellos que pueden beneficiarse de los corticoides inhalados.

Introduction

Asthma and chronic obstructive pulmonary disease (COPD) are both common, heterogeneous and usually distinct airway diseases that sometimes overlap in a particular patient. This entity, the so-called asthma–COPD overlap (ACO)[1] has attracted attention and triggered debate in recent years as evidenced by the proliferation of reviews and editorials dedicated to the topic.[2–7] GOLD and GINA define ACO as persistent airflow limitation with several features usually associated with asthma and other usually associated with COPD, and specifies that ACO encompasses different phenotypes that are likely clinical expressions of distinct underlying mechanisms.[8] Although this approach is intuitive, it is also quite imprecise because it does not take into account the relevance of each criterion for the diagnosis of ACO and it may not be useful in daily clinical practice.

ACO is difficult to define due to the lack of understanding of the underlying inflammatory mechanisms and, nowadays, it is an umbrella term that encompasses patients with COPD and eosinophilic inflammation, and smoking asthmatics with irreversible airway obstruction. In this climate of uncertainty, it is not surprising that the diagnosis of this entity remains elusive, with no defined clinical or functional criteria universally accepted. We have recently shown that ACO's manifestations are somewhere in between COPD and asthma, since these patients showed analogous demographic and inflammatory characteristics to those with asthma and functional impairment and the presence of comorbidities similar to those included in the COPD group.[9]

In this context, the Spanish Society of Pneumology and Thoracic Surgery (SEPAR) recently developed a new strategy for the identification of ACO by incorporating the new evidence generated over the last years.[10] The objective was to provide a simple and clear guidance for clinicians to help them in the identification of this entity among patients with chronic obstructive airways disease (COAD). This algorithm first requires the diagnosis of COPD based on current guidelines.[11] Once the diagnosis of COPD is established, the patient can be labelled as having ACO if a current and objectively established diagnosis of asthma is present. If this is not the case, the presence of one or two markers of Th2 inflammation – a very positive bronchodilator response (>400 ml and >15% in FEV1) and/or a significant blood eosinophilia (>300 cells/μl) – also enables the diagnosis of ACO.[10]

The aim of this study was to differentially characterize patients diagnosed with ACO according to the new SEPAR's algorithm from patients with other COAD categories (asthma and COPD patients who do not meet criteria for ACO). The characterization was made according to clinical, functional and inflammatory features and, as a secondary end-point, we assessed these variables' – in solo or in combination – capacity to distinguish ACO from asthma and COPD patients without ACO.

Material and methods

Study design

This was a multicentre and cross-sectional study. The SEPAR-ACO algorithm was applied in the CHACOS cohort of COAD patients, which has already been the subject of preliminary study.[9] Briefly, patients aged >40 years with chronic airflow obstruction (post-bronchodilator FEV1/FVC $\leq$ 0.70) and a history of physician-diagnosed asthma (non-smoking or smoking asthmatics), or COPD (non-eosinophilic or eosinophilic) who signed an informed, written consent form, were included. Patients had to be in a stable condition, free from exacerbations for at least 3 months. Exclusion criteria included primary bronchiectasis, active cancer (metastatic, progressive, or treated within the last 24 months), chronic inflammatory diseases and poor performance status.

The study was conducted in a single visit in which the researchers obtained and recorded all the clinical data into an electronic clinical research database. A blood sample was obtained to determine the number and percentage of blood eosinophil and quantification of immunoglobulin E (IgE). All investigators were asked to prospectively recruit 12 consecutive patients with COAD from their clinics: 8 belonging to the non-eosinophilic COPD and non-smoking asthma categories, and 4 belonging to the other two (Fig. 1). The study was approved by the Research Ethics Committee of the Balearic Islands (Cod: IB2499/15). Additionally, an independent Ethics committee or institutional review board for each study centre approved the final protocol.

Definitions

Chronic obstructive airway disease (COAD): patients with a FEV1/FVC post-bronchodilator <70%, regardless if it comes from COPD or asthma.

Asthma was diagnosed according to international guidelines,[8] and was classified as *non-smoking asthmatics (NSA)*: asthma patients -non-smokers or ex-smokers- with smoking history of <20