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Editorial

The Post-truth Behind the Asthma-COPD Overlap and the Orbit of Mercury: Lessons From the CHACOS Study[☆]

La posverdad detrás del solapamiento entre asma y EPOC y la órbita de Mercurio. Lecciones del estudio CHACOS

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The overlap between asthma and chronic obstructive pulmonary disease (COPD) in the same patient is one of the current challenges of research into respiratory diseases. Briefly, there are 2 distinct interpretations of this overlap that are not necessarily exclusive. One is that 2 different diseases (COPD and asthma) co-exist in the same patient; and the other is that the patient has only 1 of the diseases, but presents clinical features which departs from the conventional conception of COPD or asthma.[1,2] This debate has led to the publication of a wide range of diagnostic criteria for identifying these patients.[3]

The initial hypothesis of the CHACOS study (Characterization of ACO in Spain), sponsored by the Society of Pulmonology and Thoracic Surgery (SEPAR) and funded by the Instituto de Salud Carlos III and Chiesi Spain, was that if COPD and asthma coincided in the airway of the same patient, this would cause an inflammatory process in which the biological characteristics of each entity would merge. The objective, then, was to find unique clinical or functional features or biomarkers that would help differentiate ACO patients from those with COPD or asthma and chronic airflow obstruction (CAFO). CHACOS was a cross-sectional study in which investigators from 23 hospitals participated. In total, 292 patients >40 years of age with post-bronchodilator FEV_1/FVC <70%, were included, 94 of whom were non-smokers with asthma, 89 had COPD, and 109 were classified as having ACO, according to 2 criteria: CAFO in smoking asthmatics (44 patients) or COPD with eosinophilia $\geq$200 cells/μL (65 patients), which we called "eosinophilic COPD".

An initial analysis was performed[4] which showed that the clinical history of ACO patients did not differ significantly (symptoms measured by the Asthma Control Test and COPD Assessment Test or previous exacerbations) from patients with COPD or asthma. However, when patients were reclassified according to their inflammatory pattern as "Th2-high" ($\geq$300 eosinophils/μL in blood or $\geq$3% in sputum), or "Th2-low", 2 groups of CAFO patients emerged that did show different clinical characteristics. Consequently, this new categorization helped select patients who were candidates for treatments aimed at specific inflammatory patterns, such as inhaled corticosteroids or biological agents.

In a second study, we investigated the value and interactions of blood biomarkers of systemic inflammation (IL-6, IL-8, TNF-α, IL-17) and Th2 inflammation (periostin, IL-5, and IL-13) in patients with asthma, COPD, and ACO. A network analysis and a principal component analysis showed the inflammatory pattern of ACO to be a mixture of the patterns observed in asthma and COPD, but no single biomarkers nor any combination of biomarkers were identified that could accurately differentiate ACO from asthma or COPD.[5]

These results suggest that the ACO group (as defined in the CHACOS study) is too heterogeneous and artificial. Indeed, when the characteristics of the 2 categories included under the definition of ACO are compared, significant differences are observed, inferring a wide biological variability in the ACO group, a mishmash that includes patients with eosinophilic, neutrophilic, and mixed endotypes.[6]

A recent consensus definition of ACO includes the 2 categories mentioned above: the smoking asthmatic who develops CAFO, and the patient with eosinophilic COPD: $\geq$300 cells/μL in blood or a "strongly positive" bronchodilator test ($\geq$15% and 400 ml).[7] The CHACOS study population once again clearly demonstrates that patients with a diagnosis of ACO according to the criteria of this new consensus are indistinguishable from non-smoking asthmatics or COPD patients without eosinophilia.[8] This finding strongly challenges the adequacy of the current algorithm, and even questions the existence of a specific phenotype with perceptible clinical characteristics, even if it provides a reasonable classification of candidates for treatment with inhaled corticosteroids.

Consequently, the results of the CHACOS study support the idea that the conventional diagnostic categories based on clinical presentation are valid for differentiating clear cases of asthma ("pure Th2" inflammation) and COPD ("pure Th1" inflammation). They are, however, insufficient for identifying patient groups who exhibit mixed or atypical inflammatory or clinical features. This, then, calls for a paradigm shift in the evaluation of obstructive airway diseases that combines biological mechanisms with clinical features, and which helps identify treatable characteristics in an appropriate clinical and biological context.[9]

These about-turns are not unusual in science. Newton's equations predict fairly accurately the value of the gravitational interaction between the planets of the solar system and, in addition, how they orbit the sun. Since the end of the 19th century and the beginning of the 20th century, certain astronomical measurements established that the orbit of Mercury was shifting about 5600 arcseconds per century, a phenomenon known as "precession". However, Newton's equations predict a precession of 5557 arcseconds per century; in other words, there is a discrepancy of 43 arcseconds per century. Einstein resolved this inaccuracy with the theory of General Relativity, creating a new paradigm that contributed to the advancement of science. In the case of CAFO, the paradigm shift may come when personalized medicine is used to cross-reference the biological, clinical, and social factors of each specific patient. In the meantime, it seems reasonable to take a pragmatic attitude towards the complexity of these diseases and to tailor treatments to those traits that can be treated, with the application of medical techniques oriented to the singularities of each specific patient.[10] We believe that the collaborative effort generated during the CHACOS study must continue, and that the scientific community must examine whether this new point of view provides an objective advantage for patients, by conducting a clinical trial in which only patients with CAFO and a Th2-high profile are treated with inhaled corticosteroids (or other anti-inflammatory drugs).

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