



Editorial

Chronic Obstructive Pulmonary Disease With Eosinophilia, an Emerging Phenotype?☆



Enfermedad pulmonar obstructiva crónica con eosinofilia, ¿un fenotipo emergente?

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Chronic obstructive pulmonary disease (COPD) is diagnosed on the basis of a spirometry test, which provides indirect data on the degree of resistance offered by the airways to the passage of gas within. Currently, no histological pattern, biomarker, or even clinical criteria can give a more accurate picture of what it means to have COPD. Since it was first described, over 60 years ago, attempts have been made to differentiate COPD patients on the basis of clinical characteristics. In recent years, knowledge of the disease has increased significantly, and specific disease types which have become to be known as COPD phenotypes have been characterized. A phenotype is a description of the features presented by an individual, caused by the interaction of their genetic makeup with the environment in which they live. In all chronic diseases, the damage generated by a noxious agent is modulated by the patient's response to that molecule. The GesEPOC guideline¹ described 4 phenotypes (exacerbator, emphysema, chronic bronchitis, and overlap syndrome), with characteristics more or less defined within the COPD spectrum. It seems that this classification is set to change substantially in the next update of the guideline, since after the first edition was published, several studies have challenged some of the previously established concepts. In our opinion, 2 key points may need in-depth revision: the "exacerbator" concept and the "COPD/asthma overlap" phenotype. According to the ECLIPSE study, a patient with at least 2 exacerbations in the first year (the definition of an exacerbator phenotype) has about a 40% chance of having 1 exacerbation or none in the second year, while a patient who has been an exacerbator for the first 2 years, has a 30% chance of converting to a non-exacerbator phenotype in the third year. Furthermore, a patient who has not had any exacerbation during the first year, has about a 35% chance of having 2 in the second year.² This "phenotype" seems rather variable over time, to say the least.

When COPD presents with asthma, other problems emerge. The definition of the overlap syndrome is imprecise, no clear

biomarkers have been defined, and diagnosis is based on a series of consensus criteria with a modest grade of evidence.^{3,4} Many experts are firmly convinced that it is just 2 common diseases occurring together.

In recent years, the importance of the role of eosinophils in a generally small group of COPD patients has emerged. Eosinophilia is difficult to define. Eosinophils are cells that tend to occur in small proportions in peripheral blood, varying widely over time. In the ECLIPSE cohort, approximately 37% of subjects had persistent eosinophil levels >2% in blood samples,⁵ a percentage similar to that described in healthy subjects. However, these patients were older, predominantly male, and fewer were active smokers. They also had higher FEV1, less dyspnea, higher BODE index scores, and generally appeared to have a more benign form of the disease. Moreover, their serum levels of CXCL8, a chemokine involved in neutrophil recruitment, was significantly lower, possibly indicating some genetic modulation of the disease. If a cutoff point of 150 cells (absolute value) is applied to the analysis, the results are similar. This would suggest that clinical and biochemical characteristics differ from those of patients whose eosinophil levels in blood are less than 2%. The significant correlation with eosinophilia in sputum in COPD should also be taken into consideration, although the difficulty of using this test in routine clinical practice should be emphasized: even in a series as sophisticated as the ECLIPSE, only 138 of the 1438 patients evaluated were able to produce at least 3 valid sputum samples.

Why are blood eosinophils levels higher in some COPD patients? The basis is apparently genetic, as was shown in a study in 2 groups of patients in whom asthma was carefully ruled out. Some of these patients revealed a "genetic signature", Th2, characterized by a greater concentration of eosinophils, both in the airways and in blood, and some specific clinical features, such as rapid loss of lung function and greater post-bronchodilator reversibility.⁶ For a proposed phenotype to have clinical importance, it must be associated with a specific treatment, and this seems to be the case for COPD patients with persistent eosinophilia. In a subanalysis of the 2 studies designed to determine the efficacy of fluticasone furoate and vilanterol, the addition of inhaled corticosteroids reduced exacerbations only in patients with blood eosinophils >2%. Moreover, the effect was greater in patients with higher percentages of eosinophils, and at its height when eosinophil levels exceeded 6%.⁷

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Very similar findings were obtained from the FORWARD study, designed to examine the effect of adding beclomethasone dipropionate to formoterol in patients with severe COPD. When the 1184 FORWARD participants were divided into quartiles on the basis of their blood eosinophil level, significant differences in the reduction of exacerbations were observed in the top 2 quartiles only, with a cutoff point of 279 eosinophils/microliter.⁸ In contrast, a recent study with losmapimod, a potent inhibitor of p38 MAPK, in patients with moderate-severe COPD showed a 55% reduction of exacerbations in patients with <2% eosinophils, and no effect, or even a trend toward more frequent exacerbations in patients with more than 2% eosinophils.⁹ The protein kinase p38 MAPK is expressed in epithelial cells and macrophages activated by tobacco smoke, leading to proliferation and activation of the macrophages and neutrophils themselves, and alpha-tumor necrosis factor stimulation. Inhibiting this pathway fundamentally affects the function of both these cell types. This observation also appears to support the fact that some underlying cell pathways in COPD patients differ, depending on the presence or absence of blood eosinophilia, with the corresponding therapeutic implications.

To date, no specifically designed study has been conducted to determine the significance of blood eosinophilia in COPD, limiting the strength of the data presented. Only 1 small study has shown that treatment to reduce eosinophil levels in sputum as far as possible has a favorable impact on the reduction of exacerbations.¹⁰

To conclude, evidence is emerging for what might be a specific COPD phenotype, with differentiable clinical characteristics and specific treatment, at least in part. Obviously, many aspects still need clarification, the most important being perhaps the cutoff point for defining eosinophilia, or if an absolute value or percentage of total leukocytes would be a better measure. Nevertheless,

it seems likely that we are witnessing the birth of a new COPD phenotype.

References

1. Grupo de Trabajo de GesEPOC. Guía de Práctica Clínica para el Diagnóstico y Tratamiento de Pacientes con Enfermedad Pulmonar Obstructiva Crónica (EPOC) – Guía Española de la EPOC (GesEPOC). Arch Bronconeumol. 2012;48:2–58.
2. Hurst JR, Vestbo J, Anzueto A, Locantore N, Müllerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010;363:1128–38.
3. Postma DS, Rabe KF. The asthma-COPD overlap syndrome. N Engl J Med. 2015;373:1241–9.
4. Soler-Cataluña JJ, Cosío B, Izquierdo JL, López-Campos JL, Marín JM, Agüero R, et al. Consensus document on the overlap phenotype COPD-asthma in COPD. Arch Bronconeumol. 2012;48:331–7.
5. Singh D, Kolsum U, Brightling CE, Locantore N, Agustí A, Tal-Singer R. Eosinophilic inflammation in COPD: prevalence and clinical characteristics. Eur Respir J. 2014;44:1697–700.
6. Christenson SA, Steiling K, van den Berge M, Hijazi K, Hiemstra PS, Postma DS, et al. Asthma-COPD overlap. Clinical relevance of genomic signatures of type 2 inflammation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;191:758–66.
7. Pascoe S, Locantore N, Dransfield MT, Barnes NC, Pavord ID. Blood eosinophil counts, exacerbations, and response to the addition of inhaled fluticasone furoate to vilanterol in patients with chronic obstructive pulmonary disease: a secondary analysis of data from two parallel randomised controlled trials. Lancet Respir Med. 2015;3:435–42.
8. Siddiqui SH, Guasconi A, Vestbo J, Jones P, Agustí A, Paggiaro P, et al. Blood eosinophils: A biomarker of response to extrafine beclomethasone/formoterol in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2015;192:523–5.
9. Marks-Konczalik J, Costa M, Robertson J, McKie E, Yang S, Pascoe S. A post-hoc subgroup analysis of data from a six month clinical trial comparing the efficacy and safety of losmapimod in moderate-severe COPD patients with ≤2% and >2% blood eosinophils. Respir Med. 2015;109:860–9.
10. Siva R, Green RH, Brightling CE, Shelley M, Hargadon B, McKenna S, et al. Eosinophilic airway inflammation and exacerbations of COPD: a randomised controlled trial. Eur Respir J. 2007;29:906–13.