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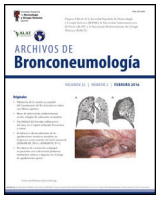

Editorial

Does the Exacerbator Phenotype in Chronic Obstructive Pulmonary Disease Really Exist?☆

¿Se puede seguir hablando de un fenotipo exacerbador en enfermedad pulmonar obstructiva crónica?

Adolfo Baloira Villar,[a,*] Marta Palop Cervera[b]

[a] Servicio de Neumología, Complexo Hospitalario Universitario de Pontevedra, Pontevedra, Spain
[b] Servicio de Neumología, Hospital de Sagunto, Sagunto, Valencia, Spain

Chronic obstructive pulmonary disease (COPD) presents in several clinical forms, which we are now beginning to characterize. One of the most important issues in the study of the natural history of the disease is the short time period analyzed in most reports. The longest follow-up to date has been the UPLIFT,[1] which lasted 4 years. This study, however, was designed as a clinical trial, so does not properly address the differentiation of patient subtypes. As the natural history of COPD probably covers several decades, conclusions obtained from studies that only examine about 5%–10% of this time may be questionable. Another major problem is that most of the patients included in these studies are in the second half of the course of their COPD, so it is difficult to determine what occurs in the early stages of the disease, when potential phenotypes could possibly have more impact on long-term progress, and when available therapeutic measures may be more effective.

Exacerbations, acute worsening of disease symptoms that require additional treatment, are a feature of COPD, and affect prognosis and quality of life. We are still far from an optimal definition and classification of these events, and no appropriate biomarkers are yet available. However, one of the key objectives of the treatments under study is to reduce these episodes. The first edition of the Spanish COPD guidelines (GesEPOC) introduced a new phenotype classification that differentiates clearly between exacerbators and non-exacerbators,[2] and this distinction is maintained in the new 2017 edition.[3] The Global Obstructive Lung Disease (GOLD) guidelines also differentiate between patients depending on the number of exacerbations, although in this case they are presented as an associated feature.[4] Both guidelines emphasize that the best predictor of an exacerbation in the next 12 months is an exacerbation in the last 12 months, a statement from which two different conclusions can be drawn: (1) having exacerbations is a characteristic that is largely independent of any other clinical variables; and (2) our present understanding of the disease is insufficient for us identify the set of variables that predispose a patient towards being an exacerbator. Let's look at these two possibilities.

If a characteristic of a disease is inherent to certain patients, that characteristic should be maintained throughout their disease history. But this is not the case with exacerbations. The ECLIPSE study showed a significant variation in the yearly exacerbation rate of patients studied over a period of 3 years.[5] For example, 39% of frequent exacerbators (2 or more exacerbations) in the first year ceased to be exacerbators in the second year. In contrast, 17% of non-exacerbators in the first year were classified as exacerbators in the second year. Being an exacerbator one year conferred a sensitivity of only 60% of being an exacerbator in the following year. The results of the SPIROMICS series may be even more interesting.[6] In this study, the pattern of exacerbations over a period of follow-up, also of 3 years, was found to vary widely. Most patients were non-exacerbators (51% in total), followed by what was termed inconsistent exacerbators, i.e., both years with and years without exacerbations (41%). Only 2% of patients had at least 2 exacerbations in each of the 3 years under study. Among the patients with more severe disease (GOLD 3 and 4), 56% were inconsistent, and only 4% were exacerbators. These results challenge the idea that the condition of exacerbator is something inherent to the patient, maintained on a regular basis in the long term.

Are we missing variables associated with exacerbations, other than previous exacerbations themselves? Lung function, even with good dispersion, appears to be a significant factor. In the ECLIPSE study, twice as many patients with GOLD 4 were frequent exacerbators as those with GOLD 2 (47% vs 22%). When exacerbations requiring hospitalization were analyzed, the percentage was almost 5-fold (33% vs 7%). Indeed, one of the most important variables was lung function, with an 11% increase in risk for each 5% decrease in FEV1, suggesting that a patient with a FEV1 of 35% predicted value has around twice the chance of being an exacerbator compared to a patient with a value of 60%.[7] This same study

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* Corresponding author.
E-mail address: adolfo.baloira.villar@sergas.es (A. Baloira Villar).

showed that a finding of more than 5% emphysema on chest computed tomography also increased the risk of at least 1 exacerbation with hospitalization by 70%. In the SPIROMICS series, the results for lung function were very similar, and the data on emphysema will be published in the near future. The data available on inflammatory biomarkers are still scant, but some studies suggest that a more inflammatory pattern (a phenotype, perhaps?) considerably increases the risk of exacerbations.[8] Eosinophils have come into the spotlight as significant players in some COPD patients, and seem set to remain there. A study of the Copenhagen series showed a 76% increase in the probability of severe exacerbations if the eosinophil concentration was greater than 340/ml.[9]

In summary, there appears to be sufficient evidence to conclude that the presence of exacerbations is a factor that changes considerably over time, and it is very difficult to predict what is going to happen in a given year on the basis of what happened in the previous 12 months, a period that, moreover, is too short for drawing conclusions. A series of variables are associated with a greater likelihood of presenting exacerbations, and lung function and emphysema may be among the most important, particularly for exacerbations requiring hospitalization, but it seems possible that the exacerbator phenotype as such does not exist. Evidence is pointing to a series of circumstances, both endogenous and exogenous, that predispose patients to exacerbations.

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