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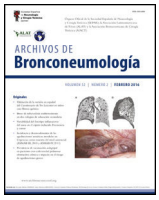

Editorial

The Future of Biological Markers in COPD☆

Futuro de los marcadores biológicos en la EPOC

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A characteristic feature of COPD is its complexity. For this reason, treatment based on symptoms and/or exacerbations may be valid as a general strategy, but lacks accuracy in the individualized management of these patients, especially if it goes beyond generic recommendations or bronchodilator therapy. However, any improvement in the initial therapeutic approach must be accompanied by greater accuracy, in order to maximize the effectiveness of a particular treatment and avoid the unnecessary costs and side effects involved in prescribing the wrong therapy. This approach is widely developed in areas such as oncology, but requires markers that can help accurately target the therapy administered. Although in COPD these markers have traditionally been functional (based on FEV1), they may also be clinical (symptoms of chronic bronchitis for the introduction of roflumilast) or radiological (volume reduction surgery). Nowadays, however, biomarkers, especially serum biomarkers, are the focus of interest.

A biomarker must primarily be able to differentiate a pathological process from a normal process, although it will only be useful if it contributes clinically relevant information that can predict risk or response to treatment. This is not easy, since for a biomarker to be implemented, it has to demonstrate up to 13 qualities (not only sensitivity and specificity),[1] the most important of which is its relationship to clinical outcomes. Most COPD biomarkers show only some of these characteristics, and very few can be defined as potentially relevant from a clinical point of view. For example, plasma fibrinogen, which plays a role in coagulation and is also a marker for systemic inflammation, has been associated with disease progression, a higher risk of exacerbations, and mortality. However, data on its usefulness is limited, since the interpretation of the results has not been clearly defined, nor has it been determined if a certain level of change justifies a therapeutic intervention. These limitations also apply to the dozens of biomarkers that have been associated with an increased risk in COPD patients (IL-8, IL-6, surfactant protein D, CC-16, microalbuminuria, leptin, adenopeptin, TNF-alpha, magnesium, red cell distribution width, bilirubin, etc.). Combining biomarkers has not helped improve these results. The ECLIPSE study identified 6 inflammatory biomarkers that differentiated the inflammatory response of smokers with and without COPD.[2] Once again, however, it is difficult to apply these results in clinical practice, as their relevance has not been established and the extent to which they can modify our therapeutic approach is unclear. These biomarkers must also have biological credibility, i.e., they must be involved in COPD pathogenesis. For example, one of the biomarkers that generated most enthusiasm and disappointment in recent years has been high-sensitivity C-reactive protein (CRP). This marker was used as an indicator of potential systemic inflammation related to airflow obstruction, and was even proposed as an indicator for prescribing certain treatments.[3] However, its value as a biomarker in COPD is limited, as it is not very specific and elevated values can be detected in many situations that frequently coexist in these patients.

Despite their current limitations in the management of COPD, biomarkers are fundamental to progress in the treatment of this disease. Promoting their use will not only allow us to advance, but will also help redesign current regimens that may be correct in a population, but incorrect in certain specific patients. For example, the negative results of the role of vitamin D in the prevention of exacerbations when analyzed in a general population (with and without vitamin D deficiency) had to be revisited when it was confirmed that positive results were obtained only when it was administered to vitamin D-deficient patients.[4,5] A similar situation arose when the effect of selective drugs in the general population of COPD was analyzed without previously identifying those with specific therapeutic targets. Similarly, the negative results of inhaled corticosteroids in lung function decline cannot be extrapolated to patients with more than 2% eosinophils in peripheral blood,[6] and the same applies to the negative results of the withdrawal of inhaled corticosteroids in the Wisdom study.[7] In fact, the lively controversy surrounding the use of inhaled corticosteroids and the value of measuring eosinophils in peripheral blood have been key to rekindling interest in this topic. But again, although eosinophils in peripheral blood (both in absolute terms and as a percentage) transmit a response signal, the level of evidence is very low (data obtained primarily from post hoc cross-sectional analyses), so in practice it is not known how a particular result should be interpreted, or if a certain level of eosinophilia justifies a therapeutic intervention. However, this is a promising area of research for either longitudinal studies with other markers that collect information from the same pathogenic route (periostin, etc.), or for studies

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with more demanding cutoff points to obtain more precise signals, which can justify, at least in these patients, more selective treatment.[8]

COPD exacerbations are another major challenge, but this is an area in which biomarkers may foreseeably be more useful in the short term. Currently, the three main challenges in the management of exacerbations are: (a) to establish the relevance of mild exacerbations, which are often difficult to differentiate from the variability of the disease itself; (b) to differentiate between different types of exacerbations, which presumably have different pathogenic mechanisms and treatment responses; and (c) to differentiate COPD exacerbations from exacerbations of other associated diseases, especially cardiovascular diseases. A systematic review[9] analyzing 134 different COPD diagnostic biomarkers pointed out serious methodological deficiencies in the study, due in part to the definition of exacerbation itself. To date, it has been reported that the elevated levels of several inflammatory biomarkers, such as neutrophils, CRP, fibrinogen, pro-calcitonin, eosinophils, IL-6, IL-8, surfactant protein D, etc., may predict an increased risk of exacerbations. However, the information provided by these biomarkers is very vague. For example, although simultaneously elevated CRP, fibrinogen and leukocytes have been associated with an increased risk of exacerbations, it has also been suggested that they may be related to associated comorbidities.

COPD patients often present comorbidities, so in clinical practice it might only be possible to correctly assess these biomarkers when they are combined with biomarkers specifically developed for these comorbidities. In fact, efforts should be made to develop biomarkers similar to NT-ProBNP/BNP (endorsed by the European Society of Cardiology), which allowed clinicians to design relatively accurate strategies for the management of both acute and chronic heart failure. Such an approach would assist in decision-making in complex patients with COPD.[10]

Conclusion: Although biomarkers in COPD are potentially promising, none has yet been identified that can clearly differentiate and accurately predict the appearance and course of the disease, the occurrence of exacerbations, the response to a particular treatment, or the risk of mortality. However, it seems clear that an essential step in the development of drugs or innovative strategies in the management of COPD is to detect specific targets that must be identified using biomarkers. It is hoped that the recent creation of the COPD Biomarker Qualification Consortium, with the participation of the FDA and the NHLBI, will help us advance in this field and use biological markers as the basis for the development of new treatments.

References

1. Beiko T, Strange CH. Chronic obstructive pulmonary disease biomarkers. Eurasian J Pulmonol. 2016;18:3–10.
2. Dickens JA, Miller BE, Edwards LD, Siverman EK, Lomas DA, Tal-Singer R. COPD association and repeatability of blood biomarkers in the ECLIPSE cohort. Respir Res. 2011;12:146.
3. Calverley P. Are inhaled corticosteroids systemic therapy for chronic obstructive pulmonary disease? Am J Respir Crit Care Med. 2004;170:721–2.
4. Lehouck A, Mathieu C, Carremans C, Baeke F, Verhaegen J, van Eldere J, et al. High doses of vitamin D to reduce exacerbations in chronic obstructive pulmonary disease: a randomized trial. Ann Intern Med. 2012;156:105–14.
5. Martineau AR, James WY, Hooper RL, Barnes NC, Jolliffe DA, Greiller CL, et al. Vitamin D3 supplementation in patients with chronic obstructive pulmonary disease (ViDiCO): a multicentre, double-blind, randomised controlled trial. Lancet Respir Med. 2015;3:120–30.
6. Barnes NC, Sharma R, Lettis S, Calverley PM. Blood eosinophils as a marker of response to inhaled corticosteroids in COPD. Eur Respir J. 2016;47:1374–82.
7. Watz H, Tetzlaff K, Wouters EF, Kirsten A, Magnussen H, Rodriguez-Roisin R, et al. Blood eosinophil count and exacerbations in severe chronic obstructive pulmonary disease after withdrawal of inhaled corticosteroids: a post-hoc analysis of the WISDOM trial. Lancet Respir Med. 2016;4:390–8.
8. Matera MG, Page C, Rogliani P, Calzetta L, Cazzola M. Therapeutic monoclonal antibodies for the treatment of chronic obstructive pulmonary disease. Drugs. 2016;76:1257–70.
9. Chen Y-WR, Leung JM, Sin DD. A systematic review of diagnostic biomarkers of COPD exacerbation. PLoS One. 2016;11, http://dx.doi.org/10.1371/journal.pone.0158843.
10. Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JGF, Coats AJS, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2016;37:2129–200.