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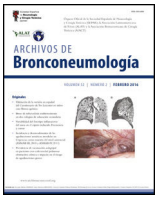

Editorial

# Personalized Medicine in Chronic Obstructive Pulmonary Disease: How Close Are We?☆

## Medicina personalizada en la enfermedad pulmonar obstructiva crónica: ¿cómo de cerca estamos?

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One of the major challenges currently facing medicine in general, and respiratory medicine in particular, is precision medicine.[1] This approach, in which each patient receives the most appropriate treatment (pharmacological or otherwise) according to their characteristics (biological, genetic, environmental), optimizing the benefit and minimizing side effects, has been confirmed as a key strategy that will undoubtedly shift our daily care pathways from evidence-based medicine to personalized medicine.[2]

Although precision medicine initially began to develop in the areas of medical oncology and hereditary diseases, data are beginning to emerge in the field of respiratory medicine that will bring us closer to this approach.[3] Indeed, now, at the end of the second decade of this century, these data are already influencing how we manage chronic obstructive pulmonary disease (COPD).

The first step toward precision medicine is the discovery of biomarkers that help us select different groups of patients who have shared therapeutic responses or disease patterns. This process began in the early years of this century and led to the concept of clinical phenotypes[4] and the development of clinical practice guidelines, such as GesEPOC, the Spanish COPD guidelines, that are based on clinical phenotypes.[5] The clinical phenotype concept is merely an intermediate step and does not fully encompass the notion of precision medicine, so more progress in this area is necessary. This is the current situation with regard to the so-called "treatable traits".[6]

The most studied treatable trait in recent years in the field of COPD is the presence of eosinophils in peripheral blood.[7] Eosinophil concentrations in peripheral blood are a reliable biomarker of response to inhaled corticosteroids (ICS)[8] in terms of reducing exacerbations compared to other therapeutic options. It is also a marker of the risk of side effects from ICS use (such as pneumonia). In fact, the number needed to treat (NNT) with ICS to prevent at least 1 moderate or severe exacerbation in the subgroup of patients with a high eosinophil count (>300 cells/mL) is less than 10. However, eosinophils only appear to play a role in the prevention of exacerbations in patients with frequent exacerbations, and the role of this biomarker in non-exacerbators is less clear.[9,10] Following the latest GOLD 2019 recommendations released at the end of last year, eosinophil counts are now one of the first examples of COPD precision medicine included in clinical practice guidelines.[11]

We also have examples of precision medicine in the field of bronchodilators. Perhaps one of the most interesting comes from a *post hoc* analysis of the POET-COPD study which investigated differences in response to 2 long-acting bronchodilators in the prevention of exacerbations.[12] In this study, patients with the $\beta_2$-adrenergic receptor (ADRB2) polymorphism Arg16Arg had a better response to salmeterol in the prevention of exacerbations compared to carriers of other polymorphisms (Arg16Gly and Gly16Gly).

More recently, a study of 64 COPD patients in an open-label crossover clinical trial[13] demonstrated that different clinical characteristics, along with gene expression and damaged-gene scores, can help predict which patients will respond significantly to the use of bronchodilators (defining this response as an increase of >100 mL in $FEV_1$ after 4 weeks of pharmacological treatment).

Finally, data from a recent crossover clinical trial[14] have shown that different pharmacological responses in COPD can be seen in different drug families, and even within the same drug family, individual response may vary considerably. In this clinical trial, which compared 2 marketed dual bronchodilator (DB) combinations, 52% of patients showed a clinically significant response in terms of $FEV_1$ to one of the DBs and 19% of patients responded similarly to the other. This effect was observed in both the previously treated population and the treatment-naïve population.[15] Unfortunately, no blood samples were obtained during this study that would help define which biomarkers indicated a higher probability of responding to one DB or the other.

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In conclusion, we are beginning to see examples of precision medicine in the field of COPD, and the results achieved with this type of approach are more promising than with "one size fits all" medicine. However, we are still only halfway there, and we will need clinical trials in the coming years to assess the real effectiveness of interventions based on similar clinical and biological patterns. To this end, the search for biomarkers and the re-analysis of large databases that contain data on the different "omics" in COPD will be equally necessary.

## Conflict of Interests

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