

COPD Therapy: Are there Too Many Pieces Lost in this Puzzle?

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Received: August 10, 2017; **Published:** August 22, 2017

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide [1]. Moreover, the overall economic burden and the need for healthcare resources are increasing over time [2]. For several years we have known that COPD is a heterogenic complex disease [3,4], and the variability of the clinical features (phenotypes) could be explained by the relatively new concept of “endotype” introduced in COPD pathogenesis. An endotype is “proposed to be a subtype of a condition defined by a distinct pathophysiological mechanism” [5], and several specific endotypes are expressed by similar phenotypes and have a different response to treatment [6].

Therapies in COPD [long-acting muscarinic antagonist (LAMA), long-acting beta agonist (LABA), phosphodiesterase inhibitors (Pis), inhaled corticosteroids (CI)] try to match the assessment of patients, according to symptoms, pulmonary function and history of exacerbations, with the main objective of relieving symptoms and reducing the risk of future adverse events [7-9]. Likewise, the new large trials are focusing on the use of bronchodilators (e. g. monotherapy vs. LABA plus LAMA; indications for ICs; triple therapy) using as surrogate endpoints clinical features rather than biochemical biomarkers [10-15] (with the exception of eosinophils [16-18]). Even though this approach improves the quality of life and indirectly reduce mortality (controlling exacerbations) [19], these are not disease-modifying therapies that would stop the progression or significantly change the natural course of COPD [20].

Furthermore, despite the progress in recent years on the identification of molecular markers for stable disease and acute exacerbations on COPD patients, the current application outside research is small, and the best marker to predict future exacerbations and response to treatment is still based on symptoms and phenotype [21]. The majority of the biomarkers, with the possible exception of α -1 antitrypsin, are not specific to respiratory disease, probably because there are many different routes through which each of these proteins or cells could be present, hindering the development of new target-specific drugs.

Precision medicine, defined as treatment targeted to the needs of individual patients on the basis of phenotypic and molecular characteristics [22], aims to improve clinical outcomes by identifying who is likely to have a better response, or fewer side effects to a specific therapy, based on an individualized assessment. It does not mean the creation of drugs unique to a patient but the ability to classify individuals into subpopulations that differ in their susceptibility to a disease, the biology, or the response to a specific treatment [23].

However, potential treatments targeting COPD pathways have failed to demonstrate their clinical benefit [24,25], probably because our understanding of COPD pathogenesis is limited. Studying of the interactions between environmental exposures, genome, biological networks and the clinical endotypes [26], would result in a better subgroups assessment in COPD, leading to an improved clinical decision and to the elaboration of new therapeutics for a more precise medicine.

Although we are far from the finish line in the race for the development of new COPD drugs, the steps back should not disappoint or discourage us. Instead, these should be taken as an incentive to be looking for another piece of the very intricate COPD puzzle. In the years to come, we will have to see the bigger picture for the good sake of our patients and the global health community, because we are going to be responsible for taking out all the information available to create therapeutic strategies intended to stopping the natural course of COPD.

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Volume 4 Issue 5 August 2017

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