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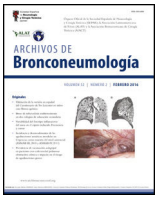

Editorial

Challenges in the Pharmacotherapy of COPD Subtypes

COPD: Definition and Challenges

It was Renne H. Laennec who close to 200 years ago first described the anatomic and clinical expression of a lung disease that he named emphysema, from the Greek "puff up" or "inflation."[1] Over the following 150 years, debates were held over the nomenclature of that chronic disease associated with bronchitis and frequently with anatomical emphysema. Finally, in the 1950s, the term chronic obstructive pulmonary disease (COPD) was introduced to encompass both bronchitis and emphysema, as they shared the presence of airflow limitation during the performance of a forced vital capacity maneuver.[2] With minimal changes, the definition of COPD had remained stable over the years with the assumption that its primary causative factor, at least in developed countries, was chronic exposure to cigarette smoke.[3] Thus, for most of the 20th century, COPD was thought to be a self-inflicted disease of elderly smokers, with the only therapy that could really alter its relentless progression being smoking cessation. Fortunately, research conducted over the last 3 decades has significantly challenged these long-held beliefs. First, population and cohort studies around the world have shown that COPD has causes other than cigarette smoking, and that there are different trajectories of lung function from birth to adulthood.[4] Second, in many persons (the "low flyers"[5]), events affecting early lung development may lead to airflow limitation starting from the first years of life or even birth. Thirdly, the combination of advanced imaging techniques, particularly computerized tomography of the chest, and high throughput "omics", has greatly enhanced basic biological studies aimed at dissecting the diverse pathobiological mechanisms, or endotypes, and clinical phenotypes of COPD. Finally, increased computer power has provided the capacity to use "big data" to integrate complex observations, thus providing a better picture of the interaction of the biological processes occurring in the transition from health to disease.

To reflect these evolving concepts, an updated COPD definition, nomenclature and taxonomy have been proposed, focused on the different causes of COPD, the structural and physiological pulmonary abnormalities that may precede full-blown clinical disease, and the heterogeneous symptoms and biological changes that can occur at any age.[6] We now know that the two major players of the former COPD definition, the absolute need for spirometric obstruction and exposure to cigarette smoke, are losing center stage to make space for a more patient-fitting definition aimed at earlier detection of the disease, precise definition of the different pathobiological pathways, and the implementation of novel therapies.

Despite these advances, COPD is still underdiagnosed, underfunded, and understudied. As a result, pharmacological therapies for COPD are currently limited. Years of randomized clinical trials, centered in older smokers with significant disease, have shown some success in improving lung function, symptoms, decreasing exacerbations and risk of death, but remain well short of the success seen in the treatment of other chronic conditions such as cardiovascular, neurological and oncological diseases. This is in part due to the fact that the recruitment of COPD patients for clinical studies has been primarily guided by COPD severity as measured by airflow limitation. However, due to the advances in our understanding of COPD, the time has arrived to conduct studies tailored to the pathobiological and clinical features of the patients to be treated (Fig. 1). In this editorial, we review some potential COPD subtypes that can be targeted with current and novel therapies, aimed at altering disease progression while simultaneously exploring their biological pathways so that more precise medications can be developed in the future.

COPD Subtypes and Associated Treatments

Genetically-determined COPD

This COPD type includes alpha 1 antitrypsin (A1AT) deficiency and the mutations of the TERT gene, that encodes for telomerase reverse transcriptase. These are the only two monogenetic variants that have been clearly shown to have a causative role in COPD. A differential diagnosis is possible through genetic testing, and specific therapies aimed at augmenting the levels of A1AT do exist. Therefore, there is an urgent need to increase testing in the general population and detect obstructed individuals who will benefit from such therapies. Further, in contrast to the current exclusion of these patients in most studies, we believe there is a need to increase their participation in trials to fully evaluate the effect, or lack thereof, of different therapies in these patients.

COPD of the Young

Recently, the term "COPD of the young" has been introduced to indicate the presence of airflow limitation in younger individuals. We recognize that for a significant number of these cases, the pathogenic processes leading to fixed airflow limitation may begin prior to adult life, as a result of pre- and peri-natal physiological or noxious stimuli such as prematurity and bronchopulmonary dysplasia (what we propose to call COPPD, chronic obstructive

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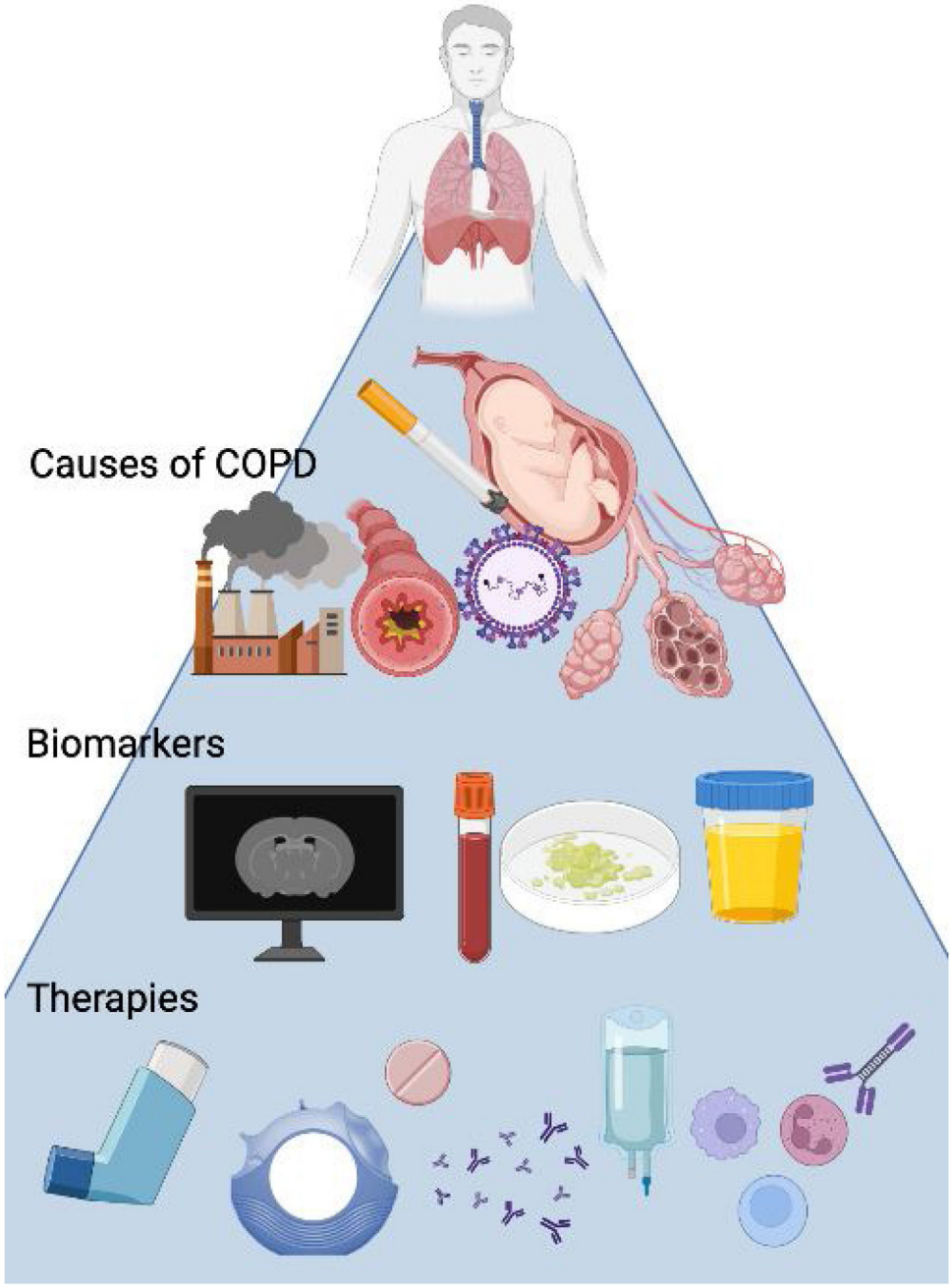

Fig. 1. COPD subtypes, biomarkers, and pharmacotherapy.

premature pulmonary disease), secondhand or maternal smoke, poor nutrition, lower respiratory tract infections, allergens.[7,8] However, it is encouraging that *post hoc* analyses of patients younger than 50 years recruited in large trials of inhaled medications have shown significant improvements in the rate of lung function decline compared to patients receiving placebo.[9] We believe there is a great opportunity to study this COPD subtype even with the current available therapies.

COPD from Asthma

Asthma present early in life, can persist until after young adulthood and become fixed airflow limitation similar to COPD.[10] In primary care, the presence of asthma requires maintenance treatment with inhaled corticosteroids (ICS) and long-acting beta2-agonists (LABA),[5,11] adding a long-acting muscarinic antagonist (LAMA) if the post-bronchodilator airflow limitation persists. In patients with uncontrolled severe asthma despite triple inhaled therapy, add-on treatment with monoclonal antibodies is usually tailored to the clinical phenotype.[12] Initial studies with monoclonal antibodies targeting interleukin-5 (IL-5) and its receptor in patients with COPD with high eosinophil counts have not been successful. However, studies using monoclonal antibodies of wider therapeutic spectrum such as anti IL-33 and thymic stromal lymphopoietin (TSLP) still hold promise in particular COPD subgroups.

COPD Dominated by Emphysema

Computed tomography (CT) has been instrumental in identifying the COPD subphenotypes of airway disease (bronchitis and

bronchiolitis) and parenchymal destruction (emphysema), which have different pathobiological manifestations. This suggests that they may be two different entities, independently of the grade of airflow limitation,[13] and not two aspects of the same disease. In fact, emphysema involves a prominent immune response with evidence of B-cell activation and lymphoid follicle formation which is absent in bronchiolitis.[14,15] The pathobiology of emphysema seems much more closely related to an activation of the adaptive immune compartment, with autoimmune features characterized by the presence of autoantibodies and T-helper type 1 (TH1) responses, which correlate with emphysema severity more than airflow limitation.[16,17] Also, emphysematous lung harbors Th1 and Th17 cells that secrete cytokines and chemokines that further enhance the release of matrix metalloproteinases, unlike bronchiolitis.[18] Therapies targeting B cells or their products are widely used in several (auto)immune diseases.[19,20] However, they are not used in COPD because of the lack of knowledge of the ideal pheno/endotype who could benefit from these therapies. Future studies should define the clinical phenotype characterized by an immune signature in blood and/or lung which could be exploited in the future as marker of COPD progression or as a tool to predict smokers who will develop emphysema *vs.* airway disease.

COPD from Biomass Exposure

This perhaps represents the most important subgroup of COPD as it is a frequent cause of COPD in large portions of the world, primarily affecting women of younger age,[21] it is a prime subtype to test the effect of our available drugs. Importantly, this COPD type primarily presents as fibrotic airway remodeling and thus represents the prototype of airway-related COPD. Its pathobiology requires intense studies so that specific therapies can be developed aimed at preventing the final fixed airway limitation so characteristic of these patients.

Conclusions

Although our understanding of the cellular and molecular mechanisms underlying COPD has improved in recent years, the persistent lack of understanding of the different COPD subtypes explains why there is no therapeutic intervention that significantly halts the disease progression (Fig. 1). Many clinical trials with negative results have led to the exclusion of potentially beneficial drugs for the treatment of COPD when the real problem was the identification of the appropriate patient population that could benefit from such therapy.[22] Thus, a shift is urgently needed to identify biomarkers and start tailoring the therapies according to the pathobiological processes underlying the different COPD subtypes. The proposed change in COPD definition, its nomenclature, and taxonomy offers an anchoring ground to target specific COPD subtypes and to use this paradigm shift for the help of COPD patients.

Authors' Contributions

FP and BC equally contributed to the writing of the manuscript.

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Competing Interests

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