Editorial

Chronic obstructive pulmonary disease: The need for differentiation and individualization of short and long-term treatment of a complex disease

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Chronic Obstructive Pulmonary Disease (COPD) is a disease characterised by enhanced inflammatory response in the airways and the lung parenchyma- mainly in the secondary lobule- to noxious particles or gases caused mainly but not exclusively by cigarette smoke. The disease is characterised by chronic obliterative bronchiolitis with endobronchial and peripbronchial fibrosis, centrilobular and/or panlobular emphysema and mucus hypersecretion of different extent. The afforementioned alterations are the base for the development of permanent and progressive airflow limitation. The structural abnormalities which are present in COPD result in disorders of the gas exchange and in abnormalities mainly of the small (pulmonary) circulation. Mechanical derangement of the lung parenchyma leads to gradual loss of any functional reserve clinically expressed initially as dyspnea on exertion and later on as respiratory failure both related to increased morbidity and mortality for each patient. Clinical diagnosis of COPD also takes into account the presence of chronic cough (productive or not) while the documentation of the diagnosis requires a post bronchodilation spirometry with an FEV_1/FVC ratio of <0.7 in a patient exposed to risk factors[1].

Exacerbations of COPD are events which occur in the course of the disease which are characterized by worsening of the patients clinical symptoms requiring changes in their medications. Exacerbations of COPD are mainly caused by respiratory tract infections (either viral or bacterial), peaks of air pollution or other unidentified factors. Exacerbations increase significantly disease morbidity (unscheduled outpatient visits, visits in emergency departments and hospitalizations). Indeed, exacerbation risk determines the clinical course of the disease, morbidity and mortality. 20% of COPD exacerbations occur in patients with moderate (GOLD 2) COPD ($50\% \leq FEV_1 < 80\%$) while exacerbation risk increases in patients with more severe COPD i.e. GOLD stage 3 ($30\% \leq FEV_1 < 50\%$) and GOLD stage 4

(FEV_1<30%). The recognition of patients more prone to exacerbations (also called frequent exacerbators) is very important since exacerbations are also related with more rapid decline of FEV_1, increased risk for hospitalizations and increased mortality. Furthermore, the identification of different pathogenetic mechanisms of different types of exacerbations could probably lead to a more targeted pharmacologic prevention and treatment[2].

However, the recognition of frequent exacerbators (defined as having at least 2 exacerbations or one hospitalization for an acute exacerbation per year) is not an easy affair since these patients might belong to different disease phenotypes, which is also related to the unmet need for the development of different therapeutic strategies. One example are patients having the so-called Asthma-COPD overlap syndrome (ACOS). This phenotype is believed to occur in 10-20% of COPD patients and is characterized by persistent airflow limitation with some characteristics of asthma such as onset of asthma before the 40th year of age, atopy, bronchial hyper-responsiveness, positive bronchodilation test, high levels of exhaled NO and sputum eosinophilia, usually with a history of cigarette smoking. For this phenotype of patients, which usually presents as a frequent exacerbator, the appropriate treatment includes inhaled corticosteroids in combination with long acting beta agonists (LABAs) with or without long acting muscarinic receptor antagonists (LAMAs), while treatment with systemic corticosteroids or high doses of inhaled budesonide during acute exacerbations. However, it is not clear whether all exacerbations in patients with ACOS are the same and steroid sensitive[3]. The identification of ACOS is even more difficult in smokers with COPD and frequent exacerbations who also have late onset asthma upon COPD. These patients also require treatment with inhaled corticosteroids.

The problem of the recognition of frequent exacerbators together with the different pathogenetic mechanisms of COPD exacerbations and the targeted pharmacological treatment that they require becomes even more complex if we consider that almost 50% of COPD patients have bronchiectasis and are colonized with abnormal and aggressive microbiome leading to the production of purulent sputum and frequent exacerbations of bacterial origin in which both inhaled and systemic corticosteroids are not indicated[4-6]. Last but not least when treating a COPD patient with frequent exacerbations, it is important to have in mind the need for different therapy when we deal with an emphysematous patient compared with a patient with predominantly chronic bronchitis[3]. It is definitely necessary to design pharmacological studies targeting the different COPD phenotypes in order to achieve a more personalized and thus more effective and safe treatment. It is a fact that pharmaceutical trials on COPD patients have led to the use of inhaled corticosteroids in up to 70% of COPD patients across Europe (in almost double doses compared to the USA) although it is known that only approximately 30% of COPD patients are frequent exacerbators[7,8]. The use of inhaled corticosteroids for long period of time is related to several adverse events such as pneumonias, osteoporosis and increased risk of bone fractures, skin thinning and bruising, tuberculosis, diabetes, cataract, oral candidiasis and many more which can affect negatively the survival of COPD patients[3,9].

While COPD is expected to be the 3rd-4th cause of death on 2020-2030 still there is no effective treatment for neither stable disease or for acute exacerbations and existing therapies present several adverse events. Furthermore, several factors affect negatively the clinical course of the disease and increase its severity. Some of them are the occurrence of diseases that can mimic exacerbations (i.e. pneumonia, pulmonary embolism and heart failure) and the presence of comorbidities (such as cardiovascular diseases, metabolic syndrome, sleep apnea syndrome, bronchial carcinoma, muscular diseases, osteoporosis, depression, combination with pulmonary fibrosis).

Studies on novel therapies such as fixed combinations of ultra LABA/LAMA have shown that withdrawal of inhaled corticosteroids is feasible without disease deterioration or increase in exacerbation frequency. This observation paves the way for the design of clinical studies targeting in different COPD phenotypes which will surely lead to the decrease of the unnecessary use of inhaled corticosteroids and to the decrease of their adverse events[10].

It is clear nowadays, that patients with COPD in the absence of ACOS must be treated with a fixed combination of either LABA/LAMA or ultra LABA/LAMA and in the case that disease control is not reached patients should be tested for the possible coexistence of bronchiectasis. Furthermore the precise COPD phenotype must be evaluated and the patient should be treated accordingly to either the presence of emphysema or chronic bronchitis. All the above should be objectives of future studies that we owe both to our patients and to scientific progress.

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