



Commentary

Gender-related Responsiveness to the Pharmacological Treatment of COPD: A First Step Towards the Personalized Medicine



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ABSTRACT

The post-hoc analysis of the data collected from the Lung Health Study supports the evolving concept that the impact of COPD may be different between men and women, and supports the hypothesis of a gender-related responsiveness to the pharmacological treatment of COPD. Specific translational studies are needed to assess the real gender-related impact of the currently available dual bronchodilation therapy on the lung function and clinical outcomes of COPD patients. This approach may represent the first affordable step towards a feasible personalized medicine.

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1. Commentary

The prevalence of chronic obstructive pulmonary disease (COPD) in women is increasing and, probably due to the changing patterns of tobacco smoking, to date it is almost equal compared to that in men (GOLD, 2017). Consequently, also the current relative risk of mortality for COPD is similar in men and women (Aryal et al., 2013). Recent findings suggested that women may be more sensitive to the detrimental effects of tobacco smoke than men. Furthermore, women suffer from more severe disease and greater small airway impairment than men, for the equivalent quantity of cigarettes consumed (GOLD, 2017). Nevertheless, most of the randomized clinical trials aimed to investigate the impact of bronchodilators in COPD recruited prevalently male COPD patients (Calzetta et al., 2016, 2017).

No consensus exists on the differences in COPD between males and females, with some researchers supporting the hypothesis of behavioral and environmental causal factors, and others sustaining that the biologic and gender-based genetic factors are more important (Aryal et al., 2013). Furthermore, inconsistent findings are currently available on the real impact of gender on the response to the pharmacological treatment of COPD (Aryal et al., 2013).

In this confusing scenario, Li et al., 2017 have carried out a post-hoc analysis of the data collected from the Lung Health Study (LHS), in order to assess whether there may be any gender-related differences in

bronchodilation related to the use of the inhaled antimuscarinic agent ipratropium bromide in patients suffering from COPD. After four months of treatment with ipratropium bromide, the improvement in forced expiratory volume in 1 s (FEV₁) was two fold higher in women than in men, and a higher percentage of female patients reached the minimal clinically important difference (MCID) compared with male patients. Intriguingly, in women the bronchodilatory effect was inversely related with the body mass index (BMI), whereas in men the impact of BMI was of little extent. The effect of ipratropium bromide remained greater in women than in men for two years, after that the greater beneficial impact on FEV₁ in women was lost. Furthermore, a higher ratio in gene expression for M₃ muscarinic receptor relative to M₂ muscarinic receptor was found in females versus males, mainly due to a lower expression of M₂ muscarinic receptor in women.

The main findings of this study (Li et al., 2017) support the evolving thought that the impact of COPD may be different between men and women. Furthermore, it seems that a gender-related responsiveness to the pharmacological treatment of COPD exists, at the least with regard to ipratropium bromide, and that BMI may play a relevant role in modulating the effectiveness of the pharmacological therapy. In fact previous findings, resulting from a large database including validated records from almost 30,000 COPD patients, indicated that the influence of BMI was associated with a higher clinical diagnosis of COPD in women compared to men, especially in overweight or obese patients, and regardless of the smoking status (Cazzola et al., 2013). Correctly, the Authors (Li et al., 2017) have also stressed that, together with the level of BMI, also comorbidities may modulate the burden of COPD in female patients. Effectively, there is a higher risk of several cardiovascular diseases, such as hypertensive disease, myocardial infarction, angina

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and coronary artery disease in female than in male COPD patients (Cazzola et al., 2012). Indeed, these risk factors should be taken into account for prescribing a safe and effective pharmacological therapy for COPD, in order to avoid the potential adverse events that characterize the bronchodilator agents and optimize bronchodilation (Calzetta et al., 2015).

The paper of Li and colleagues (Li et al., 2017) has intrinsic limitations, such as the post-hoc analytical approach of a study carried out in the 1990's, the different baseline characteristics between men and women, and the bias potentially introduced by inconsistent concomitant medications across the arms (i.e. the nicotine replacement therapy). Furthermore, LHS did not specifically collect lung samples for gene expression, but the specimens were collected from patients who underwent lung surgery resection. In any case, the findings on the expression of lung muscarinic receptors are of interest, suggesting that the gender may modulate the gene expression of M₂ muscarinic receptor, but not that of M₃ muscarinic receptor. Although the gene expression is not necessarily representative of the receptor protein expression, this modulation goes beyond what the authors (Li et al., 2017) have discussed. In fact, while M₂ muscarinic autoreceptor expressed on the preganglionic parasympathetic fibers regulates the cholinergic tone of human bronchi by inhibiting the release of neuronal acetylcholine, the activation of postsynaptic M₂ muscarinic receptor localized on the surface of the airway smooth muscle (ASM) reduces the efficacy of the β₂-adrenergic receptor (β₂-AR) signaling, and leads to increased ASM contractility (Calzetta et al., 2015). Thus, the proved pre-clinical and clinical synergistic benefits elicited by combining a long-acting β₂-AR agonist (LABA) plus a long-acting antimuscarinic agent (LAMA), the latter inhibiting the M₃ muscarinic receptor and partially also the M₂ muscarinic receptor, may have gender-specific characteristics (Cazzola et al., 2015, 2016).

Concluding, well designed translational studies are needed to assess the real gender-related impact of the currently available LABA/LAMA combinations on the lung function and clinical outcomes of COPD patients. This approach may represent the first affordable step towards a feasible personalized medicine.

Authors' Contributions

LC, EP and PR have all equally contributed in writing this commentary.

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Conflict of Interest

All the authors have no conflict of interest to declare.

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