Should the Choice of a Long-Acting Bronchodilator in the Long-Term Therapy of Chronic Obstructive Pulmonary Disease Depend Entirely on the Onset of Action?

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Both the Global Initiative for Chronic Obstructive Lung Disease guidelines [1] and the American Thoracic Society/European Respiratory Society position paper [2] recommend regular treatment with long-acting bronchodilators, including tiotropium, rather than short-acting bronchodilators, for moderate/very severe chronic obstructive pulmonary disease (COPD). These recommendations do not differentiate between long-acting β_2 -agonists, e.g. salmeterol and formoterol, and tiotropium, although β_2 -agonists and anticholinergics are distinct classes of drugs with different mechanisms of action [3].

This is the likely reason for Tennat et al. [4] to suggest that individual COPD patients may respond better to either tiotropium or salmeterol and that an acute bronchodilator test might help to choose the appropriate therapy. However, our group has documented that the bronchodilator effects of tiotropium and salmeterol, evaluated as mean changes from baseline forced expiratory volume in 1 s (FEV₁), are similar in patients with stable COPD during the first 3 h after their acute administration, and consequently the choice of prescribing a long-term therapy with a long-acting bronchodilator should not depend on the simple test of reversibility [5].

In the current issue of *Respiration*, the results of an open, randomized, crossover, clinical trial comparing formoterol and tiotropium in patients with moderate-severe COPD are presented [6]. The authors concluded that for-

moterol administered via the Aerolizer is well tolerated and results in a higher degree of bronchodilation within the first 2 h and comparable bronchodilation over a period of 12 h compared with tiotropium regarding improvement in FEV₁. These differences were maintained during a 7-day treatment and might have implications for future treatment of COPD with long-acting bronchodilators. The fact that formoterol elicited a significantly faster onset of action was not an unexpected finding. In fact, our study [7] provided strong evidence in favor of this pharmacodynamic behavior, although van Noord et al. [8] have reported that following inhalation of the morning dose of tiotropium or formoterol, the improvements in FEV₁ were comparable between the two bronchodilators until 8 h after dosing.

The question of whether FEV₁ really describes the impact of bronchodilators in COPD remains to be determined. It must be borne in mind that in stable COPD patients, a high prevalence of expiratory flow limitation exists (about 48%), even when the severity of airway obstruction in terms of FEV₁ is taken into account [9]. FEV₁ – the gold standard for assessing bronchodilator responsiveness – is only weakly correlated with patient-centered outcomes such as dyspnea [10]. In patients with COPD and expiratory flow limitation at rest, changes in inspiratory and forced vital capacities after bronchodilator use may represent an objective tool for prescribing

these drugs to attain symptomatic improvement and better quality of life, even in the absence of a significant increase in FEV₁ [11]. It is well known that regular treatment with tiotropium 18 µg once daily reduces hyperinflation [12]. We have recently documented that the acute impact of tiotropium 18 µg on the degree of pulmonary hyperinflation was faster and larger than that of budesonide/formoterol (400/12 µg) in COPD patients, although only differences in the inspiratory capacity and in the thoracic gas volume were significant between both treatments, at least after 120 min, whereas differences in the residual volume were not significant [13]. The fact that tiotropium is able to modify inspiratory capacity even after an acute administration indicates its ability to affect expiratory flow limitation in a very fast manner, and this is an important finding that allows us to question the real value of the observed changes in FEV₁. Looking

at the changes in intrathoracic gas volume, residual volume and total lung capacity in the study by Richter et al. [6], it is possible to observe that this study also confirms that the impact of tiotropium on lung hyperinflation is larger than that of formoterol even after the first drug administration. Unfortunately, they have not highlighted this important aspect and have only focused their comments on the faster improvement in FEV₁.

However, irrespective of whether or not we wish to consider only changes in FEV₁ as the most important functional outcome in COPD, it must be emphasized that the magnitude of the difference in FEV₁/area under the concentration-time curve (10–120 min) was decreased over time, confirming the fact that tolerance to pharmacologic bronchodilation occurs with long-acting β-agonists and not with inhalation of anticholinergics [14].

References

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