EDITORIAL

Anticholinergics in the Management of COPD

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In recent years our attitude towards chronic obstructive pulmonary disease (COPD) has changed dramatically from defeatist to one of hope. COPD is no longer considered an irreversible bronchial obstruction but a multifactorial disease that includes a partially reversible obstructive component.[1] In fact, depending on the evaluation criterion used, between 23% and 42% of patients present some degree of bronchodilator responsiveness,[2] and this reversibility can be clinically noteworthy in patients with severe obstruction. There are numerous mechanisms that can cause chronic airflow limitation in COPD. The thickness of airway smooth muscle is almost normal and the strength of this muscle is hardly influenced by the degree of airflow obstruction. Such obstruction is therefore believed to be caused primarily by airway wall thickening and loss of elastic load owing to destruction of lung parenchyma and parenchymal attachments surrounding the airways.[3] These irreversible structural changes enhance the effect of changes in airway muscle tone, which is regulated mainly by cholinergic activity. Overstimulation of muscarinic receptors M_1 and M_3 with acetylcholine leads to airway narrowing.[5] Airways of patients with COPD present increased cholinergic tone, as reflected by the stronger bronchodilator effect of anticholinergic drugs. Cholinergic tone increases with the severity of obstruction; therefore the increase in airway caliber depends not only on the degree of smooth muscle relaxation but also on geometric factors. The obstruction produced by structural changes, such as thickening of the airway wall, increases the relaxation–contraction effect of the smooth muscle on the diameter of the airway,[6] a factor which can be especially apparent in patients with greater airflow obstruction.

Anticholinergics act by producing a competitive blockade of acetylcholine at the muscarinic cholinergic receptors, thus inhibiting bronchoconstriction and bronchial hypersecretion, thereby increasing airflow. Two such drugs are currently available: ipratropium bromide and tiotropium. Tiotropium is a new anticholinergic bronchodilator that is administered once daily and, unlike other anticholinergics, acts through prolonged antagonism of M_3, thus sustaining airway patency for 24 hours. In patients with COPD, functional improvement after administration of bronchodilators is not always reflected in changes in forced expiratory volume in 1 second (FEV_1); in fact, it is noteworthy that FEV_1 is only weakly related to patient-reported variables such as dyspnea, exercise tolerance, and health-related quality of life (HRQL). These 3 variables are the ones that have the most impact on patients' perception of their disease and the resulting limitations; therefore, evaluation of other parameters—such as forced vital capacity, lung volume, or inspiratory capacity—may be necessary to document physiological improvement.[7] In view of the above, continuous 24-hour cholinergic blockade in the airways has important repercussions on functional, clinical, and evolution parameters of patients with COPD.

Casaburi et al[8] showed that tiotropium had superior bronchodilator efficacy compared to placebo and ipratropium—the other available anticholinergic—by measuring increased FEV_1. Furthermore, the improvement with tiotropium was sustained for the following 12 months with no tachyphylaxis. Tiotropium was also more effective compared with a placebo and ipratropium at improving dyspnea,[8] exercise tolerance, dynamic and static hyperinflation,[9] inspiratory capacity,[10] and HRQL.[11,12] Other authors such as Dusser et al[13] and Niewoehner et al[14] compared tiotropium with a placebo and found that treatment with tiotropium led to significant reduction in frequency of exacerbations and use of health care services among patients with moderate and severe COPD. The Cochrane Airways Group[15] recently prepared a meta-analysis to determine the efficacy of tiotropium, other bronchodilators used to treat stable COPD, and a placebo on the principal variables of clinical evaluation, such as exacerbations, hospitalizations, symptom scales, and lung function. The results of 9 randomized controlled trials (a total of 6584 patients) were included in the meta-analysis. According to the findings, compared with placebo or ipratropium bromide, tiotropium reduced the odds of a COPD exacerbation (odds ratio [OR], 0.74; 95% confidence interval [CI], 0.66-0.83) and related hospitalization (OR, 0.64; 95% CI, 0.51-0.82). When tiotropium was administered to patients with an annual baseline risk of exacerbations of 45% and related hospitalization of 10%, the number of patients needed to treat for 1 year with tiotropium, compared to placebo and ipratropium, was 14

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(95% CI, 11-22) to prevent 1 exacerbation, and 30 (95% CI, 22-61) to prevent 1 related hospitalization. Similar improvement was observed in the scales for quality of life and symptoms. In the same meta-analysis, for a period from 6 to 12 months, increases in FEV_1 and forced vital capacity compared to baseline values were significantly greater with tiotropium than with a placebo, ipratropium, or long-acting β_2 agonists; however, in a second analysis, the same authors reported no significant decrease in exacerbations or hospitalizations compared with long-acting β_2 agonists.[16] The conclusion of this analysis was that tiotropium, compared with a placebo and ipratropium, reduced the number of exacerbations and improved both HRQL and symptom scores of patients with moderate and severe COPD. The authors also concluded that tiotropium may slow the decline in FEV_1 characteristic of COPD. Such a delay in disease progression was reported by Anzueto et al[17] in a post hoc analysis of 2 placebo-controlled, 1-year trials. The authors concluded that patients who used tiotropium continually presented a significant long term slowing in the decline of FEV_1.

These studies have considerably extended our knowledge of the basic mechanisms of many abnormalities and limitations characteristic of COPD and of how sustained bronchodilatation can improve the state of health of patients with COPD. COPD should therefore be considered as a more complex disease, in which not only FEV_1 but also other parameters such as dyspnea, capacity for exercise, HRQL, and exacerbations must be monitored. Detailed information on the effects of tiotropium on lung function and other variables has deepened our understanding of the nature of improvements in COPD and the mechanisms by which effective bronchodilators act. Bronchodilators have been seen to produce a favorable therapeutic effect in COPD through 2 mechanisms: their bronchodilator effect (which can be evaluated only partially with bronchodilator tests) and protection of the airways against bronchoconstrictor stimuli (which confirms the importance of long-acting bronchodilators in the treatment of stable COPD).

The Global Initiative for Chronic Obstructive Disease (GOLD)[1] recommends the use of long-acting bronchodilators in the treatment of stable COPD starting with group II—although without specifying the type. Likewise, the National Institute for Health and Clinical Excellence (NICE)[18] recommends use of long-acting bronchodilators (β_2 agonists or anticholinergics) if uncontrolled symptoms persist with short-acting bronchodilators, or if the patient presents 2 or more exacerbations per year. From the economic standpoint, the societal cost of COPD is derived mainly from the health resource use by patients in more advanced stages, and especially from the cost of multiple exacerbations, the additional treatment they require, and the need for hospitalization in many such cases. Therefore interventions that reduce the severity and frequency of exacerbations, and consequently the use of healthcare services, should have a strong impact on HRQL and the cost of treatment. Any cost–effectiveness study of a given drug has noteworthy drawbacks, such as the difficulty in quantifying direct and indirect costs, the lack of stratification of subgroups according to severity of the disease, and the problem of extrapolating data from certain countries to others with different healthcare systems.[19,20] Nevertheless, some cost–effectiveness studies carried out in Spain[21,22] support treatment with tiotropium as a more cost–effective option despite high cost since clinical outcomes with tiotropium are better than with ipratropium bromide so large savings are made in hospital costs.

Inhaled bronchodilators are the mainstay drugs in COPD management thanks to their capacity to alleviate symptoms, decrease exacerbations, and improve quality of life; they also improve airflow limitation and decrease hyperinflation, thus reducing respiratory effort and improving exercise tolerance. The next line to explore is whether the combination of 2 long-acting inhaled drugs, such as β_2-agonists and anticholinergics, with few side effects and different mechanisms, could have a synergistic bronchodilator effect. Preliminary analyses[23] showed a greater bronchodilator effect for combinations of 2 drugs[24,25] than for separate administration. Analysis of the therapeutic effects of tiotropium suggests results similar to those achieved by surgical lung volume reduction. In fact, the term "pharmacologic lung volume reduction" has recently been coined,[26] thereby raising the question as to whether the long term effects of pharmacologic lung volume reduction will be similar to those of surgical lung volume reduction. It remains to be demonstrated whether the natural history of COPD can be modified by correcting the decline in FEV_1, as hoped, and whether mortality is influenced not just by FEV_1 but by other equally important factors that might indirectly affect airflow limitation. Although there is short-term (1-year) evidence[17] indicating that tiotropium may reduce the rate of decline in lung function compared with a placebo, longer follow-up is needed (at least 3 years) to demonstrate a consistent and sustained effect. We must therefore await the results of the 4-year Understanding Potential Long Term Impacts on Function With Tiotropium (UPLIFT) study in 6000 patients, to see if long-acting anticholinergics are capable of reducing and slowing the long-term loss of lung function, which is the most devastating clinical consequence of COPD.

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