Drug Treatment for Early-Stage COPD

Fanny W.S. Ko, M.D., and Gary W.K. Wong, M.D.

Chronic obstructive pulmonary disease (COPD) is a common disease with an estimated global prevalence of 11.7%, affecting almost 400 million people around the world.[1] In the United States, approximately 14% of adults 40 to 79 years of age have COPD.[2] Although the prevalence of different stages of COPD as defined by the Global Initiative for Chronic Obstructive Lung Disease (GOLD)[3] varies among different countries,[4] early-stage COPD — stage 1 disease, a facet of which is a forced expiratory volume in 1 second (FEV_1) of 80% or more of the predicted value, and stage 2 disease, which includes an FEV_1 of 50 to 79% of the predicted value — accounts for approximately 80% of persons with COPD. Although patients with early-stage COPD are the majority, there is limited information regarding the benefit of pharmacologic treatment in patients with early-stage COPD, especially in those who are relatively asymptomatic.

A subgroup analysis involving patients with GOLD stage 2 COPD who were included in the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial showed that treatment with tiotropium could reduce the rate of decline of the FEV_1 after bronchodilator use (another common feature of COPD) and the risk of COPD exacerbations.[5] Throughout the UPLIFT trial, lung function and health-related quality of life were better in the tiotropium group than in the control group. Although the subgroup analyses were prespecified, these data regarding the treatment of mild COPD were derived from a subgroup analysis of a large trial and were therefore associated with all the typical methodologic concerns of such analysis. Moreover, the UPLIFT trial did not include patients with GOLD stage 1 COPD. There are few published data for guiding the treatment for patients with GOLD stage 1 COPD, and the evidence-based treatment for patients with milder symptoms, such as those with a COPD Assessment Test (CAT) score of less than 10 (on a scale from 0 to 40, with higher scores indicating more severe disease), is not clinically directive.[6,7]

The results of the trial conducted by Zhou et al.[8] that are reported in this issue of *Journal* provide important information regarding the treatment of early-stage COPD. Zhou and colleagues studied patients who had GOLD stage 1 or 2 COPD and received tiotropium or matching placebo. This 2-year, multicenter, double-blind, randomized, controlled trial, which was conducted in China, enrolled 841 patients with COPD (367 patients with GOLD stage 1 disease and 474 with stage 2 disease) and had a primary end point of the between-group difference in the change from baseline to month 24 in the FEV_1 before bronchodilator use. The results showed a significant and clinically relevant difference of 157 ml in the FEV_1 before bronchodilator use at 24 months in favor of the tiotropium group, as compared with the placebo group. Other secondary end points, including the annual decline in the FEV_1 after bronchodilator use (but not in the FEV_1 before bronchodilator use), the exacerbation rate, and quality-of-life assessments, were significantly better in the tiotropium group than in the placebo group. Post hoc analysis also showed that the beneficial effects of tiotropium in patients with a CAT score of less than 10 and in those with GOLD stage 1 COPD were similar to the findings in the whole group.

The data gathered by Zhou et al. are particularly important for patients with GOLD stage 1 disease and those with mild symptoms because evidence about treatment for these subgroups of patients is scarce. There are concerns that more than 20% of the patients in this trial had never smoked and that some of the patients may have asthma instead of COPD. However, exposure to biomass burning is an important cause of COPD in nonsmokers in developing countries such as China.[9]

The U.S. Preventive Services Task Force (USPSTF) recently recommended against screening for COPD in asymptomatic adults[10] because there was a lack of evidence showing the benefit of early detection and treatment. How about persons with mild symptoms? Persons with mild cough productive of sputum, especially those with a long smoking history, may not seek medi-

cal advice for what seem to be innocuous symptoms. Both the USPSTF[10] and GOLD[3] recommend that persons who have a history of exposure to risk factors for COPD such as cigarette smoke and have symptoms such as dyspnea, chronic cough, or sputum production should be evaluated for COPD. Once these patients are identified, is it worth treating patients with mild or moderate disease (GOLD stage 1 or 2) with the aim of slowing the decline in lung function and reducing the frequency of exacerbations? These were secondary end points in the trial conducted by Zhou et al., and the data are probably not strong enough for clear recommendations to be made at this stage. Furthermore, the rate of COPD exacerbations requiring hospitalization in this trial was not significantly lower in the tiotropium group than in the placebo group. The rate of adherence to the trial regimen was more than 90%; outside the context of a clinical trial, patients with mild symptoms may not be as adherent to medication regimens, because their symptoms are not as bothersome.

With the development of new drugs, would treatment with another drug in the class of long-acting muscarinic antagonists (LAMAs) or long-acting beta-agonists (LABAs) or a combination of LAMAs and LABAs help to improve lung function, slow the decline in lung function, improve quality of life, and decrease the incidence of exacerbations among patients with early COPD? Early intervention and treatment for patients with diabetes mellitus and hypertension certainly lead to better outcomes. Is such an early treatment strategy possible and effective for patients with mild COPD? Further studies of the newer drugs and longer-term studies are needed to improve available treatments for millions of patients with early-stage COPD worldwide. For now, the evidence supports the judicious use of treatment in patients with symptomatic early-stage COPD or in those who are recovering from an exacerbation.

Disclosure forms provided by the authors are available with the full text of this editorial at NEJM.org.

From the Departments of Medicine and Therapeutics (F.W.S.K.) and Pediatrics (G.W.K.W.), Prince of Wales Hospital, Chinese University of Hong Kong, Shatin, China.

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DOI: 10.1056/NEJMe1707929

Moving Upstream — Anti-TSLP in Persistent Uncontrolled Asthma

Elisabeth H. Bel, M.D., Ph.D.

At least 15% of patients with asthma have a poor response to standard therapy with inhaled glucocorticoids and long-acting bronchodilators.[1] Even after nonadherence to treatment and inadequate inhalation technique are addressed, a substantial percentage of patients continue to have frequent exacerbations and hospitalizations.[2] Over the past three decades, research has led to an improved understanding of the complex biologic mechanisms of airway inflammation. This,