"This observation indicates that a ceiling effect on exercise duration may occur on leg deconditioning that can impact the potential improvements observed through improved lung mechanics," Dr. Magnussen noted.

Comorbidity Burden in Clinical Trials Versus Clinical Practice

Epidemiological studies have documented a high prevalence of comorbid conditions among patients who have chronic obstructive pulmonary disease (COPD), including hypertension, ischemic heart disease, hypercholesterolemia, diabetes, and anxiety and depression (Barr RG et al. *Am J Med* 2009; Carrasco-Garrido P et al. *BMC Pulm Med* 2009; Finkelstein J et al. *Int J COPD* 2009). The epidemiological data underscore the need to know whether clinical trial results have come from studies that adequately represent the comorbidities of COPD patients.

To examine comorbidities in clinical trials of tiotropium, Marc Miravitlles, MD, Ciber de Enfermedades Respiratorias, Barcelona, Spain, and colleagues analyzed data from 26 placebo-controlled clinical trials that were at least 4 weeks in duration. Baseline evaluation included documentation of patients' concomitant diseases and relevant medical history of the previous 5 years.

The analysis comprised 17,014 patients with COPD whose mean age was 64.6 years. The data showed that 76% of the patients were men, 84.4% was Caucasian, and baseline mean forced expiratory volume in one second (FEV_1) was 41% of predicted.

Information on baseline comorbid conditions was available for 15,375 patients. Overall, 90.4% of the patients had concomitant diseases at baseline.

The most frequently cited categories of comorbid conditions were vascular disorders (44.0%), musculoskeletal and connective tissue disorders (35.2%), gastrointestinal disorders (32.6%), metabolism and nutrition disorders (28.8%), dyslipidemia (16.7%), diabetes (9.8%), and anxiety or depression (13.7%).

Because COPD and cardiovascular conditions frequently occur together, the investigators analyzed the data for specific references to individual disorders within the broader category of cardiovascular disease. They found that 38.7% of patients had hypertension, 15.6% had conditions that were suggestive of ischemic heart disease, and 16.7% had hypercholesterolemia or hyperlipidemia.

With the exception of lipid and cholesterol abnormalities, the comorbidities of patients in the tiotropium clinical trials had prevalences that were similar to those of previous epidemiological studies, investigators concluded. Epidemiological data have generally shown higher rates of hypercholesterolemia or hyperlipidemia among patients with COPD.

Effects of COPD Therapies on Lung Function Parameters

A year of treatment with tiotropium significantly improved blood gas parameters in hypoxemic patients with severe chronic obstructive pulmonary disease (COPD), as compared with inhaled corticosteroids plus a long-acting beta-agonist (LABA), reported Maria-Christina L. Machado, MD, Federal University, Sao Paulo, Brazil.

Partial arterial oxygen pressure (PaO_2) increased significantly ($p<0.001$) from baseline and partial carbon dioxide pressure ($PaCO_2$) decreased significantly ($p<0.01$) during treatment with tiotropium versus the standard therapy. Additionally, forced expiratory volume in one second (FEV_1) increased significantly ($p<0.001$) with the bronchodilator compared with inhaled steroids plus LABA.

"These results confirm that tiotropium usage has a significant impact on lung function variables, including arterial blood gas levels in hypoxemic stable outpatients with COPD under long-term oxygen therapy," said Dr. Machado.

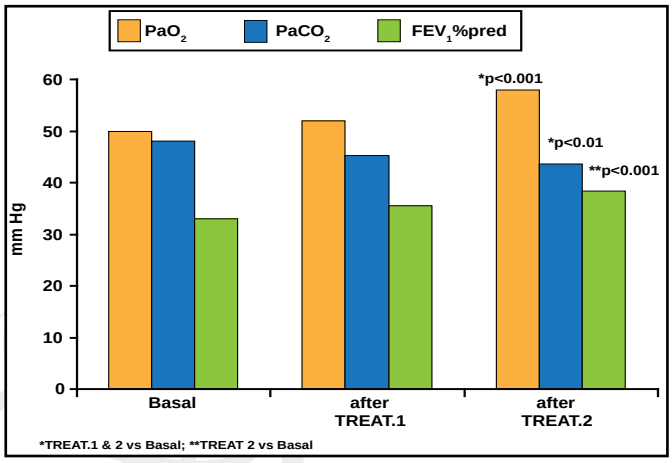
Despite the proven benefits of tiotropium on lung function in COPD patients, the agent's impact on spirometric and arterial blood gas parameters remained uncertain in hypoxemic and severe COPD, according to Dr. Machado. In an effort to resolve the uncertainty, she and her colleagues evaluated outcomes in 67 consecutive patients with severe COPD and a requirement for long-term oxygen therapy. Each patient successively completed 12 months of treatment with each of two therapies: Treatment 1: inhaled steroids plus LABA; Treatment 2: inhaled corticosteroids + LABA and tiotropium. The primary objective was to compare the relative effects of the two therapeutic strategies on three parameters of lung function: PaO_2, $PaCO_2$, and FEV_1.

Analysis of baseline characteristics showed that the patients had a mean PaO_2 of 49.9 mm Hg, mean $PaCO_2$ of 47.9 mm Hg, and mean FEV_1 of 34% of predicted. After 12 months of treatment with inhaled corticosteroids and

LABA, mean PaO_2 increased to 53.7 mm Hg and FEV_1 to 35% predicted, and $PaCO_2$ had decreased to 45.1 mm Hg.

Successively, following 12 months of treatment with inhaled steroids plus LABA and tiotropium, mean PaO_2 was 57.4 mm Hg, $PaCO_2$ was 43.3 mm Hg, and FEV_1 was 38.1% predicted. All three parameters improved significantly as compared with the standard therapy ($p<0.01$ to $p<0.001$; Figure 1).

Figure 1. Changes in PaO_2, $PaCO_2$ and FEV_1.



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These results have potential implications for health policy and economics. The public health system of Brazil has provided patients access to inhaled corticosteroids plus LABA for severe asthma since 2002, but severe COPD patients from the Federal University of Sao Paulo started having access to these medicines in 2004. However, patients with severe COPD gained access to corticosteroids plus LABA and tiotropium only in 2007, provided by the public health system from the State Government of Sao Paulo.

After July 2007, the opportunity to report pre- and post-tiotropium experiences in a cohort of severe COPD patients who were enrolled in a long-term oxygen therapy (LTOT) program for hypoxemic COPD at the Federal University of Sao Paulo was available. Study results show significant improvement in lung function, including arterial blood gas levels, after tiotropium therapy in these patients.

Additionally, because stable hypoxemic COPD outpatients experienced an improvement in all parameters after use of tiotropium and corticosteroids plus LABA and because severe hypoxemia, hypercapnia, and lung dysfunction are recognized independent markers of worst survival and usually are associated with frequent COPD hospitalization, this study suggests that the three drug combination can also bring clinical and socioeconomic benefits for these patients and health care systems.

Early Intervention in COPD

Patients with symptomatic minimal airflow limitation had significant improvement in spirometric and plethysmographic parameters following early intervention with a long-acting bronchodilator, reported Heung Bum Lee, MD, Chonbuk National University, Jeonju, South Korea.

Statistically significant improvement at 6 months was observed in forced expiratory volume at one second (FEV_1), forced vital capacity (FVC), and residual volume ($p<0.05$ to $p<0.01$). Improvement was evident as early as 4 weeks after initiation of tiotropium treatment, Dr. Lee and colleagues reported.

The rationale for the study came from recognition that chronic obstructive pulmonary disease (COPD) is a progressive condition. Early intervention could help slow or stabilize the disease process, investigators noted.

The study involved 16 patients who had minimal airflow limitation that did not meet COPD diagnostic criteria. At enrollment, the patients had a mean FEV_1/FVC ratio of 0.7-0.8, FEV_1 <80% of predicted, smoking history >10 pack-years, and dyspnea on exertion.

The patients were evaluated by spirometry and body plethysmography 2 weeks prior to starting treatment with tiotropium and again after 4 weeks and 6 months of treatment. Prescribed therapy was 18 µg tiotropium, administered once daily.

Spirometry was performed after administration of 400 µg of salbutamol. The FEV_1/FVC ratio did not change significantly from baseline. However, other parameters improved significantly, beginning as early as 4 weeks.

- Prebronchodilator FEV_1: 1.59, 1.66, and 1.74 L; $p<0.01$
- Postbronchodilator FEV_1: 1.66, 1.72, and 1.78 L; $p<0.01$
- Prebronchodilator FVC: 2.10, 2.22, and 2.31 L; $p<0.01$
- Postbronchodilator FVC: 2.24, 2.40, and 2.41 L; $p<0.01$
- Residual volume: 2.75, 2.63, and 2.16 L; $p<0.05$

Additionally, inspiratory capacity increased at 4 weeks and 6 months from baseline, but the improvement did not achieve statistical significance (1.25, 1.32, and 1.41 L; $p=0.33$).

Dr. Lee and colleagues concluded that "these results strongly support that early pharmacologic intervention can be effective in patients with symptomatic minimal airflow limitation."