Tiotropium's FEV_1 Benefit in COPD Scrutinized

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Regular use of the inhaled anticholinergic tiotropium did not significantly reduce the rate of decline in mean forced expiratory volume in 1 second in patients with chronic obstructive pulmonary disease, a large randomized, double-blind trial has shown.

However, tiotropium was associated with improvements in the secondary end points of lung function, quality of life, and rate of exacerbations, according to the findings.

The trial, known as UPLIFT (Understanding Potential Long-Term Impacts on Function With Tiotropium), randomized 5,993 patients at 490 centers in 37 countries to 4 years of therapy with either tiotropium 18 mcg inhaled once daily or placebo. They were allowed to use other respiratory medications, except inhaled anticholinergics. Patients (mean age 66 years) had moderate to very severe COPD and a mean baseline forced expiratory volume in 1 second (FEV_1) of 1.32 L after bronchodilation (48% of predicted value).

There were no significant differences between the treatment and placebo groups in the rate of decline in the mean values for FEV_1 and forced vital capacity (FVC) either before or after bronchodilation from day 30 to the end of study, lead study author Dr. Donald P. Tashkin of the University of California, Los Angeles, and his associates reported. The annual rate of decline was 30 mL/yr in both groups before bronchodilation, and 40 mL in the tiotropium group and 42 mL in the placebo group after bronchodilation.

Mean absolute improvements in FEV_1 in the tiotropium group, compared with the placebo group, were maintained at all time points after randomization, and ranged from 87 mL to 103 mL before bronchodilation and from 47 mL to 65 mL after bronchodilation. The differences were statistically significant.

The incidence of most serious adverse events was lower in the tiotropium group than in the placebo group, including a reduced risk of heart failure, COPD exacerbation, dyspnea, and respiratory failure, the authors wrote (N. Engl. J. Med. 2008;359:1543-54). In addition, the incidence rate for myocardial infarction was 0.69/100 patient-years for tiotropium, compared with 0.97/100 patient-years for placebo (relative risk, 0.71).

The incidence rate of cardiac failure, however, was 0.61/100 patient-years for tiotropium, compared with 0.48/100 patient-years for placebo (RR, 1.25).

Those findings are noteworthy, as a recently published meta-analysis showed that the use of either inhaled tiotropium or ipratropium significantly increased the risk of cardiovascular death, MI, or stroke by about 58% among patients with COPD (JAMA 2008;300:1439-50).

Pfizer Inc. and Boehringer Ingelheim GmbH, which comarket inhaled tiotropium under the trade name Spiriva and supported the UPLIFT trial, strongly rejected the findings of that meta-analysis.

The yearly rate of decline in FEV_1 observed in UPLIFT was lower than rates reported in other trials, Dr. Tashkin and associates noted, including EUROSCOP (European Respiratory Society Study on Chronic Obstructive Pulmonary Disease) and ISOLDE (Inhaled Steroids in Obstructive Lung Disease in Europe).

A potential explanation for the discrepancies is that UPLIFT allowed for prescription of all respiratory therapies at the discretion of the physicians. In addition, only 30% of patients were current smokers at baseline, compared with 38%-90% in other studies. The UPLIFT investigators also cited differences in study design, patient selection, and regional factors.

The UPLIFT trial's failure to find a difference in the rates of decline in FEV_1 might have been predictable, given previous trials' results and the fact that smoking cessation is the only intervention that meets the criteria of disease-modifying therapy, suggested Dr. John J. Reilly of the University of Pittsburgh in an accompanying editorial (N. Engl. J. Med. 2008;359:1616-8).

However, Dr. Reilly argued that the issue with UPLIFT and other recent large trials may be a signal-to-noise problem.

"There is increasing recognition that FEV_1 alone, while important, does not capture and communicate the heterogeneity of COPD," he wrote.

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