Tiotropium Backed for COPD Exacerbation

BY ELIZABETH MECHCATIE

SILVER SPRING, MD. — A Food and Drug Administration advisory panel voted 11-1 that evidence from two studies provided enough evidence to support approval of a claim that treatment with the inhaled, dry-powder formulation of tiotropium reduces exacerbations in patients with chronic obstructive pulmonary disease.

At the meeting, 11 of the 12 members of the FDA's Pulmonary-Allergy Drugs Advisory Committee also voted that data from one of those studies, the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) trial, "adequately addressed" the potential safety signals of an increased risk of stroke and adverse cardiovascular outcomes associated with this product that have been recently identified in pooled data and meta-analyses of tiotropium studies.

The dry-powder formulation of tiotropium is marketed as the Spiriva HandiHaler by Boehringer Ingelheim and Pfizer. It was approved in the United States in January 2004 for the long-term maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema. It is administered once daily; each inhalation contains a dose of 18 mcg of tiotropium, an anticholinergic.

The companies proposed that Spiriva be approved for reductions in COPD exacerbations based on the UPLIFT trial and the Veterans Affairs (VA) Exacerbations Trial. In the 6-month VA study, there were approximately 1,800 patients with COPD, most of whom were men and whose mean age was 68 years. The

Roflumilast Shows Promise For COPD

SAN DIEGO — Roflumilast improved lung function and prevented exacerbations in patients with chronic obstructive pulmonary disease with chronic bronchitis and severe airflow obstruction in a large 12-month randomized trial.

Results of the 1,568-patient, double-blind, placebo-controlled study known as the M2-125 trial indicate roflumilast is an important potential new advance in the treatment of a subset of patients with COPD, Dr. Andrew McIvor declared at the annual meeting of the American College of Chest Physicians.

Roflumilast (Daxas) is an investigational selective phosphodiesterase 4 inhibitor, a drug class that represents a novel approach to the treatment of COPD. Taken orally once daily, roflumilast targets the inflammation that's a hallmark of the disease, explained Dr. McIvor of St. Joseph's Healthcare Hamilton, Ont.

Participants in the eight-nation M2-125 trial had to have at least one documented moderate or severe COPD exacerbation during the year prior to enrollment. They were randomized to roflumilast 500 mcg once daily or placebo for 1 year, on top of background long-acting $beta_2$-agonist or short-acting anticholinergic therapy at stable doses, along with short-acting $beta_2$-agonists as needed. Long-acting anticholinergics and inhaled corticosteroids were not permitted.

The rate of moderate to severe COPD exacerbations requiring systemic steroids and/or treatment in a hospital was 1.21 cases per patient per year in the roflumilast group and 1.49 in controls, for a highly significant 18.5% relative risk reduction. Roflumilast showed a highly significant advantage, with a 33-mL increase in forced expiratory volume in 1 second (FEV_1) as compared to a 25-mL decrease with placebo over 12 months.

All-cause mortality was 3% per year in each group. Adverse events were mild in nature. The two that were more frequent in the roflumilast arm were diarrhea and weight loss, affecting 9% and 8% of patients, respectively. Nearly one-third of subjects in each treatment group withdrew from the study. The study was sponsored by Nycomed, formerly Altana Pharma, where Dr. McIvor is a consultant.

—Bruce Jancin

two primary end points—the proportion of patients with COPD exacerbations and the proportion of patients hospitalized for exacerbations—were significantly lower among those on Spiriva, compared with those on placebo: 27.9% of those on Spiriva and 32.3% of those on placebo had at least one exacerbation during the study, a significant difference (*P* value .037), and 7% of those on Spiriva had at least one exacerbation requiring hospitalization, compared with 9.5% of those on placebo, which approached significance (*P* value .056). The median time to the first exacerbation and to the first exacerbation resulting in hospitalization, secondary end points, were also reduced among those on Spiriva, compared with those on placebo.

During the study, 27.9% of those patients on Spiriva and 32.3% of those on placebo had at least one exacerbation, a significant difference.

In the UPLIFT study, a multinational, randomized, placebo-controlled, 4-year study comparing tiotropium to placebo in almost 3,000 COPD patients, the number of COPD exacerbations, which was a secondary end point, was significantly lower among those on Spiriva over 4 years, compared with those on placebo.

Also in the UPLIFT study, the risks for stroke, cardiovascular events, and mortality were all lower among those on Spiriva when compared to placebo. The FDA's analysis concluded that the UPLIFT data did not suggest an increased risk for stroke or cardiovascular events, and suggested that the data supported a decrease in mortality associated with treatment. (The risk of mortality was reduced by 27% in this study.)

The FDA usually follows the recommendations of its advisory panels. Another treatment approved for COPD, the combination of fluticasone propionate and salmeterol inhalation powder marketed as Advair Diskus, has been approved for reducing COPD exacerbations. ■