Meta-Analysis Shows Safety of LABA Combos

BY BRUCE JANCIN

KEYSTONE, COLO. — A meta-analysis of more than 23,000 asthma patients randomized to formoterol-containing regimens or to treatment without a long-acting beta-adrenergic agent showed zero asthma-related deaths and a consistent trend of fewer asthma-related hospitalizations in the formoterol/combo-treated patients.

The analysis of all 42 AstraZeneca-sponsored randomized, blinded clinical trials showed no evidence of increased risks of all-cause mortality, asthma-related deaths, or intubations in patients on combination therapy with the long-acting beta-agonist (LABA) formoterol.

Such findings support those of an earlier meta-analysis (Ann. Intern. Med. 2008;149:33-42) involving all of the more than 28,000 patients in the 66 GlaxoSmithKline-sponsored randomized trials comparing the LABA salmeterol plus an inhaled corticosteroid (ICS) versus an ICS alone, Dr. Harold S. Nelson said at a meeting on allergy and respiratory diseases.

'We've got more than 50,000 patients in clinical trials without an asthma death.'

DR. NELSON

These two meta-analyses paint a consistent picture of the safety of LABAs when used in conjunction with an ICS. It's a picture at odds with the "rather frightening" conclusions about LABA safety drawn by the Food and Drug Administration's Office of Surveillance and Epidemiology at a December 2008 meeting, said Dr. Nelson, professor of medicine at the University of Colorado/National Jewish Health, Denver.

The FDA analysis included only 1,270 of the 23,510 patients in the new meta-analysis. The regulators excluded data on non–U.S.-approved drug dosages and age groups, yielding a limited database from which they derived difficult-to-understand conclusions, the physician said at the meeting, sponsored by the National Jewish Medical and Research Center.

The FDA concerns about LABA safety arose in large part from the Salmeterol Multicenter Asthma Research Trial (SMART). But one by one, the major SMART conclusions—that salmeterol is associated with increased risk of asthma-related mortality, and that African Americans and children are uniquely vulnerable to LABA-related asthma exacerbations, as are patients homozygous for arginine at codon position 16 on the beta-2 adrenergic receptor—have subsequently been knocked down, said Dr. Nelson, who was the lead author of SMART (Chest 2006; 129:15-26) but has been among those who have taken a wrecking ball to the study.

A major problem with SMART was that compliance with ICS therapy was not monitored, and apparently many patients assigned to salmeterol weren't taking the topical anti-inflammatory agent. "There's no question that the outcomes with combination therapy in SMART were bad. The only question is was it because they weren't taking an inhaled corticosteroid," he said.

The results of the two large meta-analyses underscore the folly of much-publicized editorials calling for a new and supposedly definitive prospective trial of the safety of LABAs (Eur. Respir. J. 2009;33:3-5; N. Engl. J. Med. 2009;360:1671-2). "We've got more than 50,000 patients in clinical trials without an asthma death. … The number of patients that would be required for this new study would be somewhere between 1 million and infinity," the physician said.

The new AstraZeneca-supported meta-analysis included 13,542 patients on formoterol-containing combination therapies and 9,968 on non-LABA regimens. The relative risk of asthma-related hospitalization was 27% lower in the formoterol-treated subjects. This difference didn't achieve significance because of the small number of hospitalizations, but Dr. Nelson noted that the trend in this and in the other outcomes consistently favored formoterol combination therapy. (See box.) Also noteworthy was the finding that the asthma hospitalization rate was similar in patients on daily doses of formoterol as low as 4.5 mcg and as high as 36 mcg or more.

Regarding other concerns raised by SMART, Dr. Nelson and his coworkers showed in a 544-patient, 16-week randomized trial that patients homozygous for arginine at codon position 16 of the beta-2 adrenergic receptor did not have worse morning peak expiratory flow than those with other genotypes. Measures of lung function were consistently more favorable with salmeterol plus fluticasone than with fluticasone alone (Am. J. Respir. Crit. Care Med. 2009 Nov. 12 [doi: 10.1164/rccm.200809-1511OC]).

The supposedly greater susceptibility to asthma exacerbations seen among African Americans on LABA therapy in SMART hasn't been confirmed, either. A randomized trial involving 475 African Americans with asthma showed a mean annual asthma exacerbation rate of 0.449 cases per patient assigned to salmeterol plus fluticasone administered via the Advair Diskus device, compared with 0.529 cases per patient with fluticasone alone.

In children on formoterol and non-LABA regimens, the AstraZeneca meta-analysis showed similar asthma hospitalization rates. The same was true in the GlaxoSmithKline meta-analysis of salmeterol plus ICS versus ICS alone.

The FDA has ordered major changes to LABA product labeling, including a statement that LABAs are contraindicated without the concomitant use of asthma control medications such as inhaled corticosteroids. Dr. Nelson said that he has no quarrel with that, but he is concerned that the regulators' failure to grasp the benefits and safety of LABA/inhaled steroid combination therapy will not well serve patients and physicians. He predicted that LABA/ICS combinations are likely to become the treatment of choice as maintenance and reliever therapy for asthma, except in the United States.

"There's no need to wipe out the black box warnings on salmeterol and formoterol as monotherapy. What's needed is to say that when you put them in a container with an inhaled corticosteroid those dangers have never been shown to exist," he concluded. ■

Disclosures: *Dr. Nelson disclosed having served as a consultant to AstraZeneca Pharmaceuticals, GlaxoSmithKline, Genentech, Novartis, Schering-Plough, Sepracor, Abbott Laboratories, and Array BioPharma.*

Outcomes, Formoterol vs. Non-LABA Therapies

	Formoterol combinations	Non-LABA therapies
Patient-years of exposure	6,500	5,000
All-cause mortality (per 1,000 patient-years of exposure)	0.53	0.82
Asthma-related deaths	0	0
Asthma-related hospitalizations (per 1,000 patient-years of exposure)	12.05	16.4
Study discontinuation rate	12.7%	15.4%

Source: Dr. Nelson

ELSEVIER GLOBAL MEDICAL NEWS

Add-On LTRA May Not Help in Perennial Allergic Rhinitis

BY HEIDI SPLETE

VITALS

Major Finding: Adding a leukotriene receptor antagonist to intranasal steroids had no significant effect on nasal symptoms in perennial allergic rhinitis patients.

Data Source: Small randomized, double-blind, placebo-controlled add-on trial.

Disclosures: Dr. Esteitie had no financial conflicts to disclose. The study was funded by Merck, which markets montelukast, and the McHugh Otolaryngology Research Fund.

NEW ORLEANS — Adding a leukotriene receptor antagonist to fluticasone propionate had no significant effect on nasal symptoms in patients with perennial allergic rhinitis, based on results of a small randomized trial.

Previous clinical trials have shown that approximately half of patients with perennial allergic rhinitis obtain excellent symptom control with intranasal steroids alone, leaving the other half looking for additional relief, said Dr. Rania Esteitie of the University of Chicago.

In the study, 102 patients with perennial allergic rhinitis completed a baseline Rhinitis Quality of Life Questionnaire (RQLQ), and then received fluticasone propionate nasal spray (50 mcg per spray). The patients were instructed to use two sprays in each nostril once daily for 2 weeks (a total of 200 mcg per day).

The patients ranged in age from 18 years to 55 years (mean, 34 years), and 35% were male. The study results were presented in a poster at the annual meeting of the American Academy of Allergy, Asthma, and Immunology.

After 2 weeks, the 54 patients whose Total Symptom Scores (including non-nasal symptoms) were greater than 4 out of a total possible score of 24 (with higher scores representing worse symptoms) were randomized to use either 10 mg/day of montelukast (28 patients) or placebo (26 patients) as add-on to continuing therapy with fluticasone, the researchers reported.

Over the next 2 weeks, the patients' symptoms and quality of life continued to improve, but there was no significant difference between the montelukast and placebo groups. The median changes in Total Nasal Symptom Scores from baseline for montelukast and placebo, respectively, were –0.22 and –0.25 for sneezes, –0.52 and –0.29 for runny nose, –0.41 and –0.47 for stuffy nose, and –0.24 and –0.14 for other symptoms, Dr. Esteitie and her associates wrote.

"We expected to see an improvement in symptoms after the addition of montelukast. However, we did not see any added benefit," Dr. Esteitie said in an interview.

Although montelukast did not seem to provide additional relief for allergic rhinitis symptoms, the study was limited by the small number of patients, and additional research is needed to evaluate clinical benefits, she added. ■