

Top Asthma Studies Will Reshape Treatment

Recent papers address topics ranging from theophylline to thermoplasty to nitric oxide.

BY BRUCE JANCIN

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KEYSTONE, COLO. — Quadrupling the dose of inhaled corticosteroid was an effective strategy for prevention of asthma exacerbations, and low-dose theophylline enhanced steroids' anti-inflammatory benefits, Dr. Harold S. Nelson noted in a review of new asthma studies.

In the 403-patient study of inhaled corticosteroid dosages (*Am. J. Respir. Crit. Care Med.* 2009;180:598-602), patients who quadrupled their inhaled corticosteroid dose in response to early evidence of an exacerbation based upon morning pulmonary function testing had a 57% reduction in the relative risk of requiring oral steroids, compared with patients who made no change in their low-dose inhaled steroid regimen, Dr. Nelson said at a meeting on allergy and respiratory disease sponsored by National Jewish Health, Denver.

Although the results didn't achieve significance, he rated this trial as among the past year's highlights in the asthma literature because it answers an important, previously unresolved clinical question.

"The long-time teaching has been to double the dose of inhaled corticosteroid when a patient notices the onset of an asthma exacerbation. That strategy has been shown to be totally ineffective in two large, well-done studies," noted Dr. Nelson of National Jewish Health and professor of medicine at the University of Colorado, Denver.

Among the other highlights he identified in the recent asthma literature are:

► **Low-dose theophylline enhances the anti-inflammatory benefits of steroids:** In a study of 68 asthmatic smokers, 4 weeks of theophylline at 400 mg/day

plus beclomethasone at 200 mcg/day resulted in significantly greater improvements both in lung function and in asthma symptoms than either drug alone (*Eur. Respir. J.* 2009;33:1010-17).

The rationale for using low-dose theophylline in this setting is that cigarette smoke inhibits histone deacetylase, an enzyme that mediates the therapeutic response to corticosteroids. Low-dose theophylline increases histone deacetylase activity.

The notion that low-dose theophylline has a place in the treatment of smokers with chronic respiratory disease was reinforced in another recent study, which involved 35 patients hospitalized for acute exacerbations of COPD.

They were randomized to standard therapy—bronchodilators and systemic steroids while hospitalized, long-acting beta-agonists and inhaled corticosteroids after discharge—or to standard therapy plus 100 mg of theophylline twice daily.

At follow-up 3 months later, the theophylline group had significantly greater improvement in forced expiratory volume in 1 second than those on standard therapy. They also had more than a threefold greater increase in macrophage histone deacetylase activity, compared with baseline, and much greater reductions in inflammatory cytokine levels in their sputum (*Thorax* 2009;64:424-9).

► **Tumor necrosis factor- α inhibition for treatment of severe persistent asthma:** This double-blind trial randomized 309 patients to one of three doses of golimumab (Simponi) or placebo. The study was scheduled to run for a year but stopped early after eight golimumab-treated patients developed cancers, including five patients in the highest-dose arm. No cancers occurred in the placebo group.

There were no significant differences

between the golimumab and placebo groups in the number of severe asthma exacerbations or forced expiratory volume in 1 second at 24 weeks, the two co-primary end points (*Am. J. Respir. Crit. Care Med.* 2009;179:549-58).

► **Esomeprazole for poorly controlled asthma:** In a study carried out by the American Lung Association Asthma Clinical Research Centers, 412 patients were randomized to 40 mg of esomeprazole twice daily or placebo for 24 weeks. There were no differences in outcomes between the two study arms in terms of number of episodes of poor asthma control, nocturnal awakening, quality of life, airway reactivity, or pulmonary function. Nor did the 40% of participants with silent gastroesophageal reflux disease benefit from esomeprazole in terms of the study end points (*N. Engl. J. Med.* 2009;360:1487-99). It is clear that silent or minimally symptomatic GERD is not a likely cause of poorly controlled asthma, Dr. Nelson said.

► **Monitoring adherence to inhaled corticosteroid therapy in asthmatic children and teens:** Four methods of monitoring treatment adherence were evaluated in a 1-year study of 102 asthmatic 3- to 14-year-olds. Adherence deteriorated progressively over the course of the year. Parent and self-reports gave a wildly inflated picture of adherence. So did pharmacy dispensing records. Tracking canister weight proved to be the most practical and accurate method (*Allergy* 2009;64:1458-62).

► **Thermoplasty for severe asthma:** Thermoplasty reduces airway smooth muscle mass. The regimen entails three treatment sessions at 2-week intervals.

In Dr. Nelson's view, the verdict remains out regarding this procedure, despite a 288-patient multicenter, randomized, double-blind, sham-controlled trial. The primary study end point was clinically meaningful improvement in the Asthma Quality of Life Questionnaire

score at 52 weeks. This occurred in 79% of patients who underwent thermoplasty and 64% in the sham-procedure arm.

There were 19 hospitalizations for respiratory symptoms in the thermoplasty arm, vs. 2 in the sham-therapy arm. There were no differences between the two groups in pulmonary function tests, medication use, or asthma-free days (*Am. J. Respir. Crit. Care Med.* 2010; 181:116-24). Dr. Nelson said he'd like to see longer follow-up to better assess the procedure's long-term benefits.

► **Serum vitamin D correlates inversely with childhood asthma severity:** A study in 616 asthmatic children ages 6-14 years showed that 28% had an insufficient serum vitamin D level of 30 ng/mL or less. Serum vitamin D was inversely correlated with hospitalizations for asthma in the previous year, bronchial responsiveness to methacholine, total IgE, and circulating eosinophil counts (*Am. J. Respir. Crit. Care Med.* 2009;179:765-71).

► **Daily telemonitoring of exhaled nitric oxide in the treatment of childhood asthma:** Dutch investigators randomized 151 children with atopic asthma to management directed by daily symptom monitoring alone or in conjunction with daily telemonitoring of exhaled nitric oxide. Patients improved equally in both groups, meaning monitoring exhaled nitric oxide added nothing (*Am. J. Respir. Crit. Care Med.* 2009;179:93-7).

"There are now six studies in which exhaled nitric oxide was used to guide asthma management. None has shown a significant improvement with addition of exhaled nitric oxide," Dr. Nelson said.

Dr. Nelson disclosed serving as a consultant to Abbott, AstraZeneca, Boehringer-Ingelheim, Dey, Dynavax Technologies, Dyson, Genentech, Glaxo-SmithKline, Johnson & Johnson, MediciNova, Novartis, Schering-Plough, Sepracor, and Teva, and has received grant and research support from several of these companies. ■

Flu Vaccine May Reduce Risk of Acute Asthma Episodes

BY ROXANNA
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FROM THE NATIONAL IMMUNIZATION
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ATLANTA — Individuals with persistent asthma who received the seasonal influenza vaccination appeared to have fewer episodes of acute asthma than did those who were not vaccinated, according to Shubhayu Saha, Ph.D., of the Centers for Disease Control and Prevention's National Center for Environmental Health.

The findings corroborate current guidelines that recommend the vaccine for patients with persistent asthma, Dr. Saha said in a poster presentation at the conference, which

was sponsored by the Centers for Disease Control and Prevention.

A retrospective cohort of children and adults who met the HEDIS (Healthcare Effectiveness Data and Information Set) definition of persistent asthma was drawn from the MarketScan Commercial Claims and Encounters database. Those with chronic obstructive pulmonary disease, cystic fibrosis, and emphysema were excluded from the study. Of 138,935 individuals in the cohort, 22% received the vaccine in the 2006-2007 flu season (August 2006 to March 2007).

Bivariate comparisons indicated that acute asthma

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Major Finding: The odds ratio of having acute asthma episodes for the vaccinated group was 0.78, when the instrumental variables method was used.

Data Source: A retrospective cohort of 138,935 children and adults with persistent asthma drawn from the MarketScan Commercial Claims and Encounters database, 22% of whom received the seasonal flu vaccine.

Disclosures: Dr. Saha said the findings do not represent the official position of the CDC. He reported no conflicts of interest.

episodes requiring an emergency department visit and/or hospitalization during the follow-up period were more frequent in those who received the vaccine (4.9%) than in those who did not (4.0%). However, those in the treatment group also were younger, had higher Charlson comorbidity scores, used more con-

troller medications, and had more acute asthma episodes in the past.

To control for potential confounding where asthma patients with poorer prognoses also were more likely to get the flu vaccine, the investigators used two methods (instrumental variables and propensity score matching) to obtain un-

biased estimates of the effect of the vaccine on acute asthma episodes. Each approach yielded similar and statistically significant results—results that were contrary to those of the bivariate comparisons.

Controlling for age, sex, region, health plan, comorbidity, and past asthma exacerbation, the two methods gave odds ratios of 0.78 and 0.7 for the vaccinated group having acute asthma episodes.

The odds ratios "show [the] significant protective effect of the influenza vaccination in reducing acute asthma episodes among individuals with persistent asthma in a population with employer-based health insurance," Dr. Saha said. ■