Refractory Asthma Persists Even With Guidelines

BY NANCY WALSH
New York Bureau

TORONTO — A substantial proportion of patients with severe, refractory asthma are unable to become well controlled despite the availability of updated guidelines, even in subspecialty care, according to Dr. Amandeep S. Gill of the Medical College of Wisconsin, Milwaukee.

The National Asthma Education and Prevention Program's Guidelines for the Diagnosis and Management of Asthma have been updated periodically since they were first published in 1991, reflecting changes in evidence-based data since that time, with the latest revision being released in 2007.

However, little is known about the effect of the guidelines on the prevalence of severe refractory asthma. To assess the impact, a study was undertaken of 172 patients referred to subspecialty management programs in two Midwestern cities, comparing disease status at presentation and after 1 year of guideline-based care that included education and minimized barriers to care.

A total of 103 patients were seen in an asthma clinic at Case Western Reserve University, Cleveland, and 69 patients in a disease management program at the Medical College of Wisconsin, Milwaukee. Asthma morbidity was assessed retrospectively for the previous year, while patients were being managed in primary care, and prospectively for the subsequent year while they were receiving subspecialty care.

Controlled asthma was defined as:

- Symptoms no more than twice per week.
- Nocturnal symptoms fewer than two times per month.
- Short-acting bronchodilator use no more than twice per week.
- No interference with normal activities.
- Forced expiratory volume in 1 second (FEV_1) at least 80% of predicted.
- No more than one exacerbation per year requiring oral corticosteroids.

In contrast, severe refractory asthma was classified as the requirement for high-dose inhaled corticosteroids and a long-acting β-agonist with or without oral steroids and/or omalizumab (step 5 or 6 pharmacotherapy in the guidelines).

The mean age at entry among patients from both cities was 48 years, and the mean duration of asthma was 17 years. More than three-quarters were female, and more than half were African American or Latino.

Patients With Features of Refractory Asthma

	Cleveland (n = 103)		Milwaukee (n = 69)	
	At entry	At 1 year	At entry	At 1 year
Daily symptoms	80%	32%	65%	35%
One or more urgent visits	82%	48%	68%	42%
Extra controlling medications (long-acting ß-agonists, leukotriene modifiers, theophylline)	50%	92%	65%	83%
FEV_1 below 80%	55%	17%	42%	25%
Unable to decrease steroids	n/a	20%	n/a	33%

Source: Dr. Gill

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At presentation, 20% of patients from Cleveland and slightly more than 30% of patients from Milwaukee had severe refractory asthma, yet only 34% and 46%, respectively, were on appropriate medications for their level of disease severity. Only 54% and 62%, respectively, were able to demonstrate the proper use of a metered-dose inhaler.

After 1 year of subspecialty treatment, the numbers of urgent care and emergency department visits fell significantly in both groups, but many other disease characteristics did not improve significantly.

Overall, the percentage of patients whose asthma was well controlled improved from less than 10% to 20% after 1 year. However, 32% of patients still had severe persistent disease at 1 year, and half of those whose disease was not well controlled were receiving high-dose inhaled corticosteroids and a long-acting β-agonist.

Furthermore, at 1 year, 40% of patients from both cohorts were using the maximum available level of pharmacotherapy but could not achieve well-controlled status.

"Even when asthmatics are well educated in self-management techniques and have access to continuity of care and appropriate medications, more than three-fourths are unable to become well controlled," Dr. Gill wrote. ■

PPI Therapy Does Not Help Asthma Without GERD Symptoms

BY NANCY WALSH
New York Bureau

TORONTO — Treatment with a proton pump inhibitor did not improve asthma control in patients with poorly controlled asthma and minimal or no symptoms of gastroesophageal reflux, according to results from a large study presented at an international conference of the American Thoracic Society.

Gastroesophageal reflux disease (GERD) is a common problem in patients with asthma, with small studies reporting a prevalence of reflux in 32%-84% of asthmatics. Proton pump inhibitor (PPI) therapy is commonly added to therapy in asthma, adding to the overall cost of treatment, but the effect of suppression of gastric acid on asthma symptoms remains unclear, according to Dr. Mario Castro of Washington University School, St. Louis.

Uncertainty about the role of GERD in asthma derives from observations that about half of asthmatics without symptoms of GERD have been shown to have abnormal reflux and about half of asthmatics who have abnormal reflux shown on pH probe studies do not have symptoms of the disease, Dr. Castro explained. "GERD symptoms can mimic symptoms of asthma, and we wanted to know how to distinguish them and how best to treat them."

Recent guidelines released by the National Heart, Lung, and Blood Institute (NHLBI) of the National Institutes of Health suggested that, even in the absence of GERD symptoms, consideration should be given to evaluation and possible treatment with PPI for patients with poorly controlled asthma. This was a consensus-based recommendation.

To gain additional data to strengthen the recommendation, the Study of Acid Reflux in Asthma (SARA) was undertaken with funding from the NHLBI and conducted by the American Lung Association's asthma clinical research centers, a national 20-center network dedicated to improving asthma care.

"SARA included only patients with minimal or no symptoms of GERD, because we felt that any patient with moderate or severe GERD should, by definition, be receiving a PPI—and, in this trial, there was the possibility that they would receive placebo," Dr. Castro said.

Aside from determining whether PPI therapy could improve asthma symptoms in those patients, SARA also sought to determine whether ambulatory pH probe monitoring could identify patients with asymptomatic GERD who might benefit from suppression of gastric acid.

The study design called for a 2- to 8-week run-in period, during which patients underwent pH probe monitoring and, if not contraindicated, methacholine challenge testing. They then were randomized to receive esomeprazole, 40 mg/day, along with stable doses of inhaled corticosteroids (equivalent to at least 400 mg fluticasone/day) and long-acting β-agonists if needed.

Poorly controlled asthma was defined as two or more occasions of a 30% or greater decline in peak expiratory flow from baseline, the need for oral prednisone, the requirement for acute intervention (an emergency department visit), or the need for more than four puffs of rescue medication.

Another investigator, Dr. W. Gerald Teague of the pediatric asthma center at Emory University, Atlanta, described the participants' baseline characteristics . "A total of 412 patients were randomized, … data from 10 patients were lost in Hurricane Katrina." Of those remaining, 199 received placebo and 203 received esomeprazole.

Overall, the groups were comparable. Mean age was 42 years, and 50% were white and 38% were black. In the placebo group, 28% were male and 20% were former smokers. In the esomeprazole group, 36% were male and 15% were former smokers. About half of the patients in both groups had required use of rescue medications during the previous year, and the same number had required courses of oral prednisone. Asthma control also was equivalent in the two groups, with a mean Asthma Control Questionnaire (ACQ) score of 1.9 in the placebo group and 1.8 in the PPI group.

Lung function also was comparable, with a forced expiratory volume in 1 second (FEV_1) at 78% of predicted in the placebo group and 76% of predicted in the esomeprazole group. There were no differences in post-albuterol response, forced vital capacity, or bronchial hyperresponsiveness. On pH probe testing, 40% of patients in both groups were positive for GERD.

"We were surprised, but when baseline asthma characteristics were analyzed according to whether or not patients were positive for GERD on pH probe testing, there was very little effect," Dr. Teague said. In both GERD and non-GERD groups, 80% had required rescue medicine, ACQ scores were 1.9, and Asthma Quality of Life scores were 4.6, he reported.

"Overall, we saw no treatment effect in either group," Dr. John G. Mastronarde, a pulmonologist at Ohio State University Medical Center, Columbus, and director of the university's asthma center. The number of episodes of decrease in peak flow was 1.7/person per year in the placebo group and 2.1/person per year in the esomeprazole group. The number of episodes requiring urgent care was 0.7 in the placebo group and 0.6 in the esomeprazole group.

Some study data have suggested certain subgroups, such as patients with episodes of nocturnal awakening and those with a body mass index greater than 30 kg/m^2, might respond to PPI treatment. However, those were no different between the placebo and active treatment groups.

Lung function as measured on FEV_1, peak flow, and tests of bronchial hyperresponsiveness also showed no effects of treatment, nor did patient-centered outcomes such as ACQ scores, even in patients with positive pH probe tests, Dr. Mastronarde said.

"In summary, asymptomatic GERD is common in patients with poorly controlled asthma, but PPI therapy with esomeprazole does not improve asthma control or lung function in patients with minimal or absent symptoms of GERD. … Ambulatory pH probe testing did not seem to identify any subgroups of patients who might benefit from PPI testing in terms of asthma control," he said.

"The NIH guidelines suggest that we consider evaluation and treatment in patients with poorly controlled asthma on adequate controllers even without symptoms of GERD, but this study would suggest that PPI therapy has no effect on control and is not indicated," Dr. Mastronarde noted. "Also, there doesn't seem to be any reason to do pH probe testing on poorly controlled asthmatics, because even if they are positive, it doesn't predict who will respond to PPI treatment." ■