Panel Backs Thermoplasty Device for Asthma

Conditions are stipulated for approval, reflecting some concern about longer-term safety and efficacy.

BY ELIZABETH MECHCATIE

GAITHERSBURG, MD. — A Food and Drug Administration advisory panel on voted 6-1 that a novel device that uses thermal energy to ablate smooth muscle in the airway during bronchoscopy could be approved under certain conditions, as a treatment for severe, persistent asthma in people aged 18 years and older.

At the meeting, members of the FDA's Anesthesiology and Respiratory Therapy Devices Panel agreed that there was reasonable evidence that the device was safe and effective for this indication, but stipulated several conditions for approval, reflecting concerns about the need for longer-term safety and efficacy data.

The conditions included requiring the manufacturer to enroll all patients treated with the device after approval in a registry, which would follow the durability of the therapeutic effects and safety; and not using the device in patients with impaired coagulation or in those who are on anticoagulant medication, because hemoptysis was reported in six treated patients in the pivotal study.

Other conditions for approval were that physicians who use the device be adequately trained, and that patients not be retreated with the device until clinical trial data on the effects of retreatment are available. The panel also unanimously recommended postmarketing studies to further evaluate the safety and effectiveness of the device, with end points that include emergency department visits for respiratory symptoms, corticosteroid requirements, asthma exacerbations, and hospitalizations.

Components of the Alair Bronchial Thermoplasty system include a radiofrequency (RF) generator and a single-use catheter with an electrode basket at the tip that delivers RF energy to surrounding tissue. Treatment results in clinical improvements in people with severe asthma by using thermal energy "to reduce the airway smooth muscle responsible for airway constriction in asthma patients," according to the device's manufacturer, Asthmatx.

The device uses thermal energy to reduce the smooth muscle that is responsible for airway constriction occurring in patients with severe asthma.

The pivotal study conducted in six countries compared treatment with the device in 190 patients to sham bronchoscopy in 98 patients (where the catheter was deployed, without RF). Patients, whose median age was 41 years, had severe persistent asthma that was "not well controlled" (30%) or "very poorly controlled" (70%), and required high doses of inhaled corticosteroids and long-acting beta agonist therapy. Treatment was administered during three separate outpatient bronchoscopies 3 weeks apart. Each procedure took about 30 minutes, according to Asthmatx.

The primary end point was the average of the changes in 6-, 9-, and 12-month Asthma Quality of Life Questionnaire (AQLQ) scores, a patient self-administered validated questionnaire, from baseline. Scores increased among patients in both groups, but the average of the three scores was 0.21 points greater among those in the active treatment group, compared with those in the sham group, which just missed statistical significance, according to the FDA's analysis. The largest effects of treatment were seen at U.S. study sites, but in Brazil, improvements in the scores were somewhat higher among those in the sham group, which panelists agreed was a concern. Some panelists thought this may have been due to the free maintenance medications received by all the patients enrolled at the Brazil sites, possibly reflecting greater compliance with medication therapy.

Some of the study's secondary end points, including rates of severe exacerbations after treatment; days lost from work, school, or other daily activities due to asthma symptoms; and emergency department visits for respiratory symptoms, were lower among those treated with the device. Nearly 79% of those on Alair had a change in the AQLQ score of at least 0.5 (which the company said is the threshold for a clinically meaningful change), compared with 64.3% of those on sham treatment, the company reported.

Respiratory-related events, including asthma symptoms, were higher among those in the device-treated patients during the treatment phase (from the time of the first bronchoscopy through 6 weeks after the third bronchoscopy) but lower than among those in the sham group after that time. A total of six patients (3%) treated with the device had hemoptysis, which typically occurred soon after the procedure and was self-limited; one patient developed severe hemoptysis 31 days after treatment. But there were no cases in sham-treated patients. There were no treatment-related deaths or withdrawals for worsening asthma in the study.

Although the primary effectiveness end point in the pivotal study was not met, panelists supporting approval said they considered some of the secondary end points to be clinically relevant.

The panel generally agreed that the device appeared to be safe, but that long-term safety should be monitored, including the potential for dysplastic changes and malignancy in the treated areas. (There has been no evidence of structural abnormalities or neoplasia during up to 5 years of follow-up, according to Asthmatx.)

Panelist Dr. Sharon Rounds, chief of pulmonary/critical care at Providence (R.I.) Veterans Affairs Medical Center, said that despite her concerns about the regional variability in the effectiveness results, she was impressed with the secondary end points and that "on balance, the risks are offset by the reasonably effective nature of the intervention." A long-term study following patients for at least 5 years after treatment is needed to monitor treatment durability and potential long-term sequelae of "undoubted damage to the epithelium and other components of the airway wall, in addition to bronchial smooth muscle," she added.

Another panel member, Dr. Polly Parsons, director of the pulmonary and critical care medicine unit at the University of Vermont, Burlington, agreed that the evidence provided "reasonable assurance" that the device was safe and effective, but added it would be a concern if it was used in patients "beyond those defined as eligible for the trial."

The panelist who voted against approval, Dr. Sandra Willsie, a pulmonologist in Overland Park, Kan., said, "I believe there's promise here, but I have misgivings in view of the very impressive placebo effect that the data are robust enough."

The FDA usually follows the recommendations of its advisory panels. If the agent is approved, the company plans further studies, including one that will follow patients in the pivotal trial through 5 years, and will provide didactic and interactive training for physicians. ■

Patients With Asthma at Increased Risk for Depression

BY KATE JOHNSON

MONTREAL — Primary care patients with asthma face a significantly increased risk of developing depression, compared with the nonasthmatic population, according to the findings of a large, longitudinal study.

Furthermore, the combination of asthma and depression carries significantly increased mortality, reported Dr. Paul Walters of the Institute of Psychiatry, King's College, London.

Taken together, the findings suggest that it may be useful for family physicians to consider screening their asthmatic patients for depression, he said at the annual meeting of the North American Primary Care Research Group.

In a previous study, Dr. Walters and his colleagues found that asthma was the third-largest predictor of antidepressant prescriptions in the United Kingdom (Br. J. Psychiatry 2008; 193:235-9).

"We expected there to be a higher rate of antidepressant use with chronic illnesses, but we didn't expect to see this with asthma," he said.

The current longitudinal cohort study, designed to explore the association between asthma and depression, identified 11,275 asthmatic patients with no history of depression and an equal number of control subjects, matched for age and sex from the United Kingdom's General Practice Research Database.

During a 10-year follow-up period, the incidence of depression was significantly higher in the group with asthma, compared with controls (22.4 versus 13.8 per 1,000 person-years); after adjustment for age, sex, chronic illness, and smoking, the odds ratio for depression among asthmatic patients remained elevated (1.5).

Looking next at the asthmatic patients only, the researchers noted those with comorbid depression had an elevated mortality ratio (1.87), compared with those with asthma alone. "So, if you've got asthma and you're depressed, then you're almost twice as likely to die than if you've just got asthma," explained Dr. Walters.

He acknowledged that "we don't have any information on cause of death, so we're not able to say if it was due to asthma-related reasons or depression-related reasons or a combination of both."

For clues as to why asthmatic patients face a higher risk for depression, the researchers explored the issue of disease severity, using medication use as a marker. Comparison of asthmatic patients who were depressed to those who were not depressed showed no significant differences in the use of medication overall, suggesting that disease severity was similar in both groups, he said.

The biggest difference between the groups was in their frequency of primary care visits (8.3 visits a year for depressed patients versus 5.3 for nondepressed patients). One possible explanation for this association may be that "if a patient goes to their [general practitioner] more often, they're more likely to get their depression diagnosed," Dr. Walters said in an interview.

Another explanation, however, is that a patient's subjective experience of asthma symptoms might be quite different from objective medical assessments. "It could be that the objective measure of asthma, the peak flow rate, doesn't actually relate to how the person with asthma feels, so the depression comes because their asthma doesn't feel like it's getting better."

Dr. Walters had no conflicts of interest to report. ■