

Bronchoscopic Procedure Targets Severe Asthma

BY MIRIAM E. TUCKER

Senior Writer

PHILADELPHIA — An investigational bronchoscopic procedure marketed as Bronchial Thermoplasty may offer an effective, safe, and permanent treatment for the small proportion of patients with severe asthma who cannot be controlled with conventional medications, Dr. Alan R. Leff said at the annual meeting of the American College of Physicians.

About 10% of all asthma patients have severe disease that is inadequately responsive to available treatments with β -agonists, corticosteroids, or leukotriene modifiers. All of these therapies are directed at the active disease state, rather than modifying the underlying disease process.

Bronchial Thermoplasty, in contrast, aims to permanently “undo” the contractile ability of airway smooth muscle, thereby preventing bronchoconstriction, explained Dr. Leff, professor of medicine, pediatrics, anesthesiology, and critical care at the University of Chicago.

Dr. Leff is a consultant for Asthmatx Inc. (www.asthmatx.com), which is currently recruiting adult patients with severe asthma for a phase III trial of its Bronchial Thermoplasty system, Alair.

The treatment involves application of heat via the bronchoscope into all airways with diameters of 3 mm or more, and selectively ablating the airway smooth muscle—which is particularly heat sensitive—while preserving other tissues.

All experimental evidence points to the fact that this is safe because mammalian airway smooth muscle is vestigial and has no function. “In neither human nor animal studies has there been anything to indicate that airway smooth muscle really does anything ... the goal of all asthma treatment is to get as little airway smooth muscle tone as possible. Clearly, asthma patients are better off the less tone they have.”

In a preliminary study, 16 patients with mild to moderate asthma underwent Bronchial Thermoplasty. The procedure was well tolerated, with side effects that were transient and typical of effects commonly observed after bronchoscopy.

Reductions in airway hyperresponsiveness occurred in all 16 patients, with a mean increase of 2.37 doublings of the PC₂₀ (provocative concentration of methacholine causing a 20% fall in forced expiratory volume in one second) at 12 weeks. At 1 year post procedure, the mean increase in PC₂₀ was 2.77 doublings, and at 2 years, it was

2.64 doublings, Dr. Gerard Cox and his associates reported (*Am. J. Respir. Crit. Care Med.* 2006;173:965-9).

Data from daily diaries collected for 12 weeks indicated significant improvements over baseline in symptom-free days, morning peak flow, and evening peak flow measurements, while spirometry measurements remained stable throughout the study period, said Dr. Cox and his associates from the institute for respiratory health at McMaster University, Hamilton, Ontario.

Preliminary trials of Bronchial Thermoplasty have been conducted in patients with only mild to moderate disease (forced expiratory volume in 1 second greater than 80% predicted) to ensure that the treatment would not exacerbate human asthma, which cannot be replicated in an animal model.

In follow-up data that have now reached a duration of 3 years, there has been continued improvement, with no worsening seen. “It’s looking like the improvement is pretty much a permanent thing,” Dr. Leff noted. Several clinical studies are now underway in patients with moderate to severe asthma, the group for whom the treatment would be indicated.

Dr. Leff said the procedure is typically accomplished in two or three half-hour sessions, roughly the length of an average bronchoscopy.

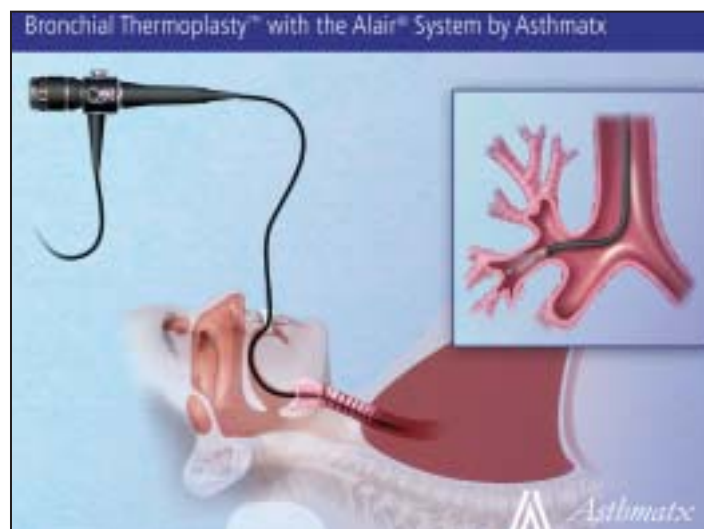
In an editorial that accompanied the published article, Dr. Elisabeth H. Bel said the study “suggests that Bronchial Thermoplasty has the potential to become a re-

alistic therapeutic option in chronic asthma not satisfactorily controlled with pharmacotherapy.”

However, Dr. Bel, doctor of medicine and philosophy in the pulmonology department at Leiden University Medical Center, the Netherlands, added two cautionary notes. For one, the long-term consequences of the procedure are unknown, and it is possible that problems such as permanent widening of the large airways, chronic infections, or increased airway wall collapsibility might appear over time. “Therefore, long-term observation of subjects undergoing this procedure is mandatory,” she said.

Secondly, it is not yet clear to what degree Bronchial Thermoplasty targets the peripheral airways and it may well be that inadequate treatment of those airways may be the primary reason that patients with refractory asthma do not respond satisfactorily to inhaled therapy. If patients refrain from pharmacotherapy because of symptom improvement following this procedure, the distal airways could become even more inflamed and obstructed than before. Long-term data from the ongoing studies involving patients with moderate to severe asthma will shed further light on the issue.

“Bronchial Thermoplasty should never be applied without proper anti-inflammatory pharmacotherapy in these patients,” said Dr. Bel. He has been a speaker at meetings financed by several pharmaceutical companies and was on the advisory board for Merck, Sharpe & Dohme Ltd. until 2005.



In the outpatient procedure, a flexible bronchoscope delivers thermal energy to accessible airways of 3-10 mm in diameter.



The treated airway did not constrict with methacholine (arrow shows untreated airway).

Use of Steroids in Premies May Reduce Lung Function Later

BY PATRICE WENDLING

Chicago Bureau

MONTREAL — A diagnosis of chronic lung disease of prematurity did not predict reduced lung function in childhood in a study of long-term respiratory outcomes in children born extremely prematurely.

But the study provided evidence that postnatal corticosteroid use is associated with reduced childhood lung function, although a causal relationship could not be definitively established, Ms. Lucia Smith said at the Seventh International Congress on Pediatric Pulmonology.

The lack of association of reduced lung function with chronic lung disease of prematurity (CLDP) runs contrary to traditional opinion in the literature, which suggests lung function is significantly reduced in children with CLDP.

“Most older studies have tended to compare children with CLDP with term controls rather than preterm controls, but

our results are consistent with results in recent studies in CLDP cohorts,” Ms. Smith said in an interview.

The cross-sectional study included 126 children born between 1992 and 1994 at a mean gestational age of 27 weeks, who were recruited from the New South Wales, Australia, neonatal intensive care units database, and 34 age-matched controls who were born full term. The average weight at birth was 862 g for the children born prematurely, compared with 3,420 g for the children born full term.

Medical records available for 104 preterm children showed 37 (35.5%) had CLDP, defined as any infant who was still dependent on supplemental oxygen at 36 weeks, and 46 of the 104 (44%) had received systemic corticosteroids at any time during the initial neonatal intensive care unit stay immediately after birth.

There was no difference in spirometry between children born prematurely who were diagnosed with CLDP as neonates

and those who were not, said Ms. Smith, a PhD candidate at the University of Sydney, New South Wales, and her associates.

Spirometry values were significantly lower in the preterm group, compared with controls: mean forced vital capacity, 96% vs. 102%; mean forced expiratory volume in 1 second (FEV₁), 85% vs. 95%; and forced expiratory flow at 25%-75% of forced vital capacity (FEF_{25%-75%}), 72% vs. 91%.

The preterm children who received postnatal corticosteroids had significantly lower flows than those who did not (FEV₁, 82% vs. 88% and FEF_{25%-75%}, 65% vs. 78%). These measures were within “normal limits” for lung function, Ms. Smith said.

In a regression analysis, cumulative steroid use, age of first steroid dose, birth weight, gestation, number of days intubated, or maximum oxygen concentration had no relationship with lung function.

“Our results highlight the fact that the definition of CLDP uses an arbitrary cut off of oxygen requirement at 36 weeks’ gesta-

tional age,” Ms. Smith said. “There are no standardized criteria to assist the decision to cease supplemental oxygen, and it is likely to differ in different neonatal units.”

In reality, a number of children in the non-CLDP group may have only just come off supplemental oxygen by 36 weeks, she said. Likewise, some in the CLDP group may not have needed oxygen at 36 weeks, Ms. Smith added, thus the lack of association of reduced lung function with CLDP.

In a question-and-answer session, audience members called the corticosteroid data fascinating, but posited that a number of the preterm children must have fallen outside of “normal” limits for lung function. Ms. Smith said there was a range of results, particularly in airway flow, both for those preterm children who received steroids and those who did not. Data that were not presented indicate that fitness and exercise tolerance are markedly reduced in the entire preterm group, with results less than 50% of those in the control group, she said.