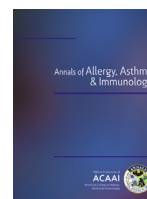




ELSEVIER

Contents lists available at ScienceDirect



Guest editorial

Bronchial thermoplasty: Safe for our severe asthma patients?

Bronchial thermoplasty (BT) is a new bronchoscopic procedure to treat the airway of adult patients with severe asthma who have not achieved control with inhaled corticosteroids and long-acting bronchodilators. The procedure is delivered by the Alair system (Boston Scientific) by applying controlled thermal energy to the airway walls in 3 bronchoscopy sessions with the goal of reducing airway smooth muscle hypertrophy in these patients. In 3 randomized control trials, BT has been shown to improve asthma control,^{1,2} improve quality of life,^{1,3} and reduce severe exacerbations.³ As a result, it was approved by U.S. Federal Drug Administration (FDA) in April 2010. The FDA also required additional post-approval studies to evaluate the long-term durability and safety. The data from 1 of these trials are reported here.⁴

In the short term, BT can cause transient worsening of asthma symptoms immediately after the procedure. The worsening of asthma induced by BT can be severe enough to require hospitalization in approximately 10% of patients.^{2,3} In addition to exacerbations, atelectasis of the treated airways, lower respiratory infections, and hemoptysis can occur.^{2,3} However, all of these postprocedural adverse events resolve quickly with standard therapy. Therefore long-term results are needed to establish the appropriate risk–benefit ratio for patients considering BT.

The long-term effectiveness and safety of BT has recently become available for patients originally treated in controlled trials.^{1–3} The 5-year safety of BT in the first randomized trial (Asthma Intervention Research [AIR] trial) involving patients with moderate to severe asthma was reported in 2011.⁵ Thomson et al⁵ were able to follow 45 of the 52 treated patients and demonstrated that the rate of respiratory adverse events, including severe exacerbations and healthcare utilization, and lung function were stable up to 5 years later. In the larger AIR2 trial with a sham-control group, Castro et al⁶ reported in 166 of 190 patients that received BT a stable reduction in health care utilization and unchanged lung function 2 years after treatment.⁶ Recently, 5-year safety data of the AIR 2 trial was presented by Wechsler et al,⁴ which again confirmed a sustained reduction in severe exacerbations and respiratory adverse events. The AIR2 trial did not provide long-term follow-up in the sham-treated patients beyond 1 year.

In this issue of the journal, Pavord et al report the 5-year outcome from 14 of 15 participants who underwent BT in the Research in Severe Asthma trial.⁷ The number of the participants in this trial was significantly smaller than the AIR2 trial, but the patient's underlying asthma symptoms were more severe, they had lower lung function (average forced expiratory volume in 1 second 64% vs 78% in AIR2), and they required oral corticosteroids more frequently (47% vs 3% in AIR2). Despite the more severe asthma, Pavord et al demonstrated that the rate of respiratory events and

forced expiratory volume in 1 second remained significantly reduced over 5 years after BT compared with baseline. An impressive overall 72% reduction in respiratory-related hospitalizations was seen over 5 years compared with the pre-BT rate.

Is BT safe over the long term for patients with severe asthma? Given the data from this report and other large randomized trials, BT does appear to be safe long term. Each of these studies demonstrated no increase in adverse events or decline in lung function or other serious event (such as bronchiectasis or stricture) over 5 years since receiving BT. The current report extends the long-term safety results to those with more severe disease, albeit with conclusions based on a small sample size. Conversely, clinical stability over 5 years after BT does not necessarily equate with long-term efficacy. For ethical reasons, the patients in the control group were not followed for 5 years (AIR followed the control group to 3 years), so true efficacy cannot be addressed. Regardless, the lack of change in maintenance inhaled and oral corticosteroid use (or possibly even reduction) together with the sustained control of asthma risk (as reflected by the reduced health care utilization) allows the clinician to conclude that BT is indeed safe and efficacious over the long term.

Major hurdles for BT lie in the appropriate patient selection, procedural training of the bronchoscopists, and coverage of the cost of the treatment by third-party payers. Three years after receiving FDA approval, BT still has not disseminated widely in our treatment of severe asthma because of the uncertainty of appropriate patient selection and coverage of costs. Even though BT has been shown to be effective in most patients, whether all patients responded equally is not clear. Currently patients with severe persistent asthma on high-dose inhaled corticosteroids and long-acting beta-agonists that remain uncontrolled (as reflected by 2 or more courses of systemic corticosteroids in the prior year) despite optimization of environmental control measures and treatment of comorbidities are appropriate to be evaluated for BT. Patients that have an implanted electronic device, are on anticoagulants or antiplatelet agents, or have known sensitivity to medications required to perform bronchoscopy should be excluded. Studies from the Severe Asthma Research Program^{8,9} and from the use of biological therapy with antibodies to interleukin-4, interleukin-5, and interleukin-13^{10–12} demonstrate that patients with severe asthma are quite heterogeneous in their clinical and biological phenotypes and how they respond to certain treatments. Currently no validated biomarkers exist measuring airway smooth muscle or other phenotypic predictors of response to BT. However, a prospective observational study to evaluate clinical, biological, and imaging biomarkers predictive of response to BT in patients with severe refractory asthma is ongoing in the United States (ClinicalTrials.gov Identifier: NCT1185275). Because BT requires specific procedural skills and can exacerbate asthma in these

Disclosures: Authors have nothing to disclose.

patients with severe disease, standardization of procedural training is important because this treatment disseminates outside of specialized centers. Lastly, from our own experience third-party payers currently agree to cover the cost of BT in only approximately 50% of cases. The availability of category I CPT procedure codes for BT in 2013 is a step forward for broader coverage of this novel treatment. Fortunately, these long-term data provide us reassurance that BT is safe and effective for these patients with difficult to control asthma.

Kaharu Sumino, MD, MPH*

Mario Castro, MD, MPH*

*Division of Pulmonary and Critical Care Medicine
Washington University School of Medicine

St Louis, Missouri

castrom@wustl.edu

References

- [1] Cox G, Thomson NC, Rubin AS, et al. Asthma control during the year after bronchial thermoplasty. *N Engl J Med.* 2007;356:1327–1337.
- [2] Pavord ID, Cox G, Thomson NC, et al. Safety and efficacy of bronchial thermoplasty in symptomatic, severe asthma. *Am J Respir Crit Care Med.* 2007;176:1185–1191.
- [3] Castro M, Rubin AS, Laviolette M, et al. Effectiveness and safety of bronchial thermoplasty in the treatment of severe asthma: a multicenter, randomized, double-blind, sham-controlled clinical trial. *Am J Respir Crit Care Med.* 2010;181:116–124.
- [4] Thomson NC, Rubin AS, Niven RM, et al. Long-term (5 year) safety of bronchial thermoplasty: Asthma Intervention Research (AIR) trial. *BMC Pulm Med.* 2011;11:8.
- [5] Castro M, Rubin A, Laviolette M, Hanania NA, Armstrong B, Cox G. Persistence of effectiveness of bronchial thermoplasty in patients with severe asthma. *Ann Allergy Asthma Immunol.* 2011;107:65–70.
- [6] Wechsler ME, Shah PL, Niven R, et al. Benefits of bronchial thermoplasty persists out to 5 years in patients with severe asthma. *Am J Respir Crit Care Med.* 2013;187:A3868.
- [7] Pavord ID, Thomas NC, Niven RM, Corris PA, Chung KF, Cox G, et al. Safety of bronchial thermoplasty in patients with severe refractory asthma. *Ann Allergy Asthma Immunol.* In press.
- [8] Moore WC, Bleecker ER, Curran-Everett D, et al. Characterization of the severe asthma phenotype by the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. *J Allergy Clin Immunol.* 2007;119:405–413.
- [9] Moore WC, Meyers DA, Wenzel SE, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med.* 2010;181:315–323.
- [10] Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet.* 2012;380:651–659.
- [11] Corren J, Lemanske RF, Hanania NA, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med.* 2011;365:1088–1098.
- [12] Wenzel S, Ford L, Pearlman D, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med.* 2013;368:2455–2466.