

Bronchial Thermoplasty for Severe Asthma

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Bronchial thermoplasty (BT) is a novel treatment of patients with severe asthma who continue to be symptomatic despite maximal medical treatment. It aims to reduce the smooth muscle mass in the airways by delivering controlled thermal energy to the airway walls during a series of three bronchoscopies. Randomized controlled clinical trials of BT in severe asthma have not been able to show a reduction in airway hyperresponsiveness or change in FEV₁ but have suggested an improvement in quality of life, as well as a reduction in the rate of severe exacerbations, emergency department visits, and days lost from school or work. Strict inclusion and exclusion criteria of these trials resulted in the elimination of patients with severe asthma who experienced more than three exacerbations per year. Therefore, the generalizability of this treatment to the broader severe asthma population still needs to be determined. The short-term adverse events consist primarily of airway inflammation and occasionally more severe events requiring hospitalization. Long-term safety data are evolving and have shown thus far clinical and functional stability up to 5 years after BT treatment. Additional studies on BT are needed to establish accurate phenotyping of positive responders, durability of effect, and long-term safety.

Keywords: asthma; treatment; bronchoscopy

Asthma is a syndrome of nonspecific airway hyperresponsiveness, inflammation, and intermittent respiratory symptoms triggered by infection, environmental allergens, or other stimuli. Severe asthma is characterized by persistent symptoms, increased medication requirement, airflow limitation, and frequent exacerbations. Although severe asthma is estimated to be present in less than 10% of all patients with asthma, these patients exhibit the greatest morbidity and consume an overwhelming proportion of health care costs (1). The mainstay of asthma therapy is corticosteroids, short- and long-acting β_2 -receptor adrenergic agonists, and leukotriene antagonists administered at doses and frequency outlined in the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) *Guidelines for the Diagnosis and Management of Asthma* (2). These therapies reduce inflammation or decrease airway narrowing by relaxing the airway smooth muscle, but do not prevent the chronic structural changes that occur in the airway smooth muscle in asthma. In addition, their effectiveness is not uniform in this population, highlighting the need for additional options. Several alternative therapies have been studied in the last decade,

particularly biologics with immunomodulatory activity (3–7). Recently, a new approach for the treatment of severe asthma has been approved: bronchial thermoplasty.

BRONCHIAL THERMOPLASTY AS THERAPY FOR SEVERE ASTHMA

Bronchial thermoplasty (BT), a new concept in the treatment of asthma, aims to reduce the airway smooth muscle (ASM) mass with the goal of diminishing bronchial constriction and ameliorating asthma symptoms. The reduction in ASM is accomplished by delivering controlled thermal energy to the airway walls during a series of three bronchoscopies. The thermal energy is delivered via the Alair system (Boston Scientific, Natick, MA), which consists of a radiofrequency electrical generator and a single-use catheter with an expandable four-electrode basket at its distal tip (Figure 1). The electrical energy delivered through the electrodes is converted into heat when met with tissue resistance. A continuous feedback to the energy generator ensures close regulation of the degree and time of tissue heating to the desired prespecified temperature of 65°C. This temperature was arrived at on the basis of experimental animal and human data with the goal of achieving a reduction, rather than eradication, of the ASM mass and minimizing damage to structures adjacent to the airways (8, 9). The energy is applied for 10 seconds at each treatment site and is estimated to reach 18 W (10). Bronchial thermoplasty is delivered in a systematic fashion to airways located beyond the mainstem main bronchi and are on average 10 to 3 mm in diameter with exclusion of more distal airways.

MECHANISM OF ACTION

The precise role of the smooth muscles in the airways has been a subject of much debate. Some investigators argue that ASM are embryonic remnants with no essential function and have dubbed them “the appendix of the lung” (11). Others suggest that ASM may play a vital role in the regulation of bronchomotor tone, immunomodulation, and the promotion of airway remodeling (12–14). Furthermore, it is believed that ASM play a role in the distribution of ventilation and propulsion of mucus in healthy subjects (15, 16).

In asthma, the airway smooth muscle is the main effector of bronchoconstriction in response to various stimuli, including several inflammatory mediators (17, 18). The smooth muscle can also promote inflammation by producing a variety of cytokines and chemokines such as CXCL10 (IP-10) and fractalkine that participate in an autocrine loop (17, 18). Mast cells perpetuate this inflammatory cascade as they have been shown to associate with airway smooth muscle in patients with asthma (19, 20). Upon activation and degranulation, they also produce a number of cytokines and mediators such as IL-4 and leukotriene B₄ that can contribute to airway hyperresponsiveness and promote the increase in airway smooth muscle mass (18, 21, 22). Therefore, airway smooth muscle is an active participant in the inflammatory response and contributes to asthma exacerbations.

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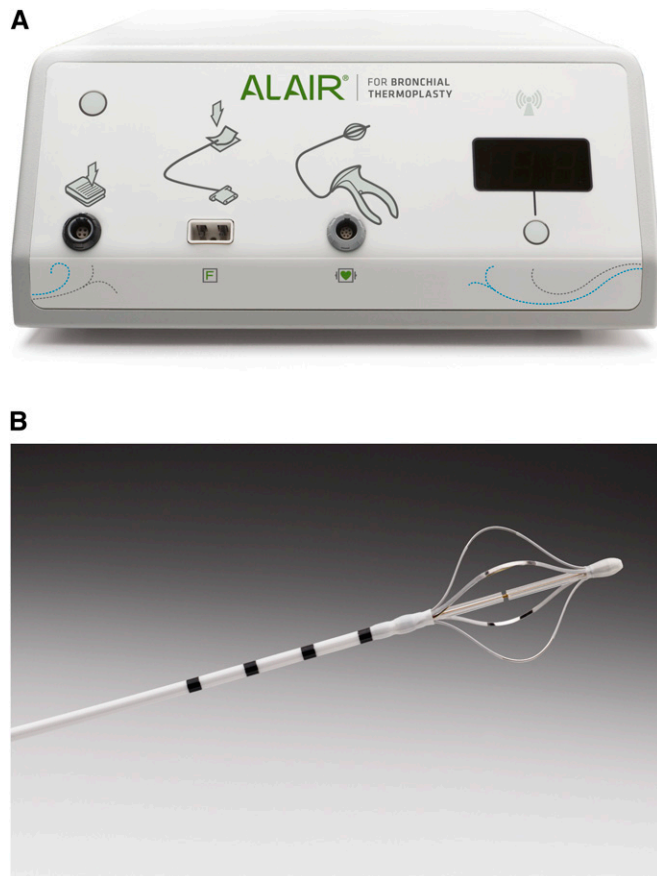


Figure 1. The Alair bronchial thermoplasty system. (A) The radiofrequency energy controller. (B) The thermoplasty catheter with a distal shaft marked at 5-mm intervals and an expandable basket carrying four electrodes.

Bronchial thermoplasty has been shown to reduce the ASM mass via radiofrequency ablation in healthy animal and human airways (8, 9); whether the reduction in ASM mass can be reproduced in the airways of patients with asthma or is the only mechanism responsible for the clinical benefits seen in patients with severe asthma requires further study. Alternative or contributing mechanisms of BT may include modification in the extracellular matrix that can lead to fixed airway structure, reduction of mucus gland hyperplasia with an accompanying decrease in mucus production, or change in the autonomic tone of the airway.

Another question regarding the mechanism of BT is its ability to achieve clinical response despite its limited application to the larger lobar and segmental bronchi (>3 mm in diameter) with exclusion of distal and smaller airways. Studies have shown that inflammation in small airways is a prominent contributor to the pathophysiology of asthma (23, 24); the favorable clinical results of BT point to the complexity of asthma pathogenesis and the possibility of proximal airways' contribution to it. Some have postulated that ASM contractility is governed by pacemakers within the proximal airways and that thermoplasty ablates these controlling centers, leading to the distal effect (25). Alternatively, there may be a phenotype of subjects with asthma with a more prominent component of large airway inflammation and obstruction, making them more likely to benefit from BT.

EFFICACY AND SAFETY

Early work in BT tested its mechanism of action and effect in a canine model. Danek and colleagues applied bronchial thermoplasty on the airways of 11 healthy dogs and found persistent and

significant reduction in treated airway responsiveness to local methacholine (MCh) provocation (8). More importantly, these investigators performed necropsy and histological examination of the untreated and treated airways at various time points, up to 3 years, and found persistent ASM reduction in the treated airways with no evidence of regeneration. The thermal injury was limited to the bronchial wall and the immediate peribronchial region, and the extent of ASM reduction correlated with the improvement in airway hyperresponsiveness.

Three additional canine studies validated these findings by using high-resolution computed tomography for objective measurements of the airway diameter and reproducing the decreased airway sensitivity to a range of concentrations of MCh and variable degrees of lung inflation (26–28). A more recent study attempted to identify the cellular mechanism underlying the loss of function in bovine ASM after exposure to heat similar to that of thermoplasty and found direct dose-dependent disruption of the actin–myosin interaction leading to immediate loss of ASM cell function with no evidence of apoptosis, autophagy, or necrosis (29).

A summary of study results employing BT in human patients with asthma is shown in Table 1. The first feasibility and short-term safety study on human airways was performed in 2005 in eight patients without asthma scheduled for surgical resection for proven or suspected lung cancer (9). Subjects underwent BT to the lobe to be removed 2 to 3 weeks before surgery. The treated airways were reexamined at the time of surgery and exhibited mild erythema, edema, or blanching within 2 weeks of the treatment. Histological examinations of resected airways showed an average of 50% reduction in the smooth muscle mass of the treated airways compared with nontreated airways. None of the patients experienced adverse events or change in medical care. This study paved the way to clinical studies in patients with asthma.

The first study evaluating bronchial thermoplasty in asthma enrolled 16 patients with stable mild to moderate asthma and found a significant reduction in airway hyperresponsiveness for up to 2 years after the procedure but no change in FEV₁ (30). Short-term adverse events were common but were mainly mild and composed of airway inflammation that either resolved spontaneously or required a temporary increase in asthma medications. Chest computed tomography performed 1 and 2 years after the procedure did not show evidence of bronchiectasis, bronchial wall thickening, or other parenchymal changes.

BT was then studied in a randomized, controlled, multicenter trial that enrolled 112 patients with moderate to severe persistent asthma (the Asthma Intervention Research [AIR] Trial) (31). There was an improvement in asthma symptoms but no reduction in airway hyperresponsiveness or change in FEV₁. Once again, the major adverse event was mild airway inflammation in the postprocedure period; however, subjects who underwent BT in this study had a higher hospitalization rate (six vs. two hospitalizations in the BT vs. control group, respectively). Given the nonblinded design and lack of a sham arm in this study, its findings were limited because of a possible placebo effect.

In 2007, a small randomized study enrolled 32 patients with severe symptomatic asthma (refractory asthma) in an attempt to establish the safety of BT in this population (the Research in Severe Asthma [RISA] Trial) (32). Patients were receiving higher doses of inhaled corticosteroids and oral prednisone than in previous studies (see Table 1). Seven hospitalizations due to worsening asthma symptoms occurred, during the treatment period, in 4 of 15 BT subjects. Lobar collapse occurred in two subjects, with one requiring bronchoscopic aspiration of mucous plugs. Persistent improvement in asthma symptoms and decrease in rescue medication use were seen in the BT group up to the 1-year follow-up period of the study (-25.6 ± 31.2 vs. -6.1 ± 12.4 puffs/7 d; $P < 0.05$).

TABLE 1. SUMMARY OF CLINICAL TRIALS ON BRONCHIAL THERMOPLASTY

Study	Study Design	Number of Patients	Severity of Asthma, ICS Dose ($\mu\text{g}/\text{d}$)*, and OCS Dose (mg/d)	Duration of Follow-Up	Outcomes with Improvement	Outcomes with No Change	Short-term Adverse Events	Long-term Adverse Events
Cox and colleagues (30)	Prospective, nonrandomized	16	Mild to moderate stable asthma, ≤ 1800 , 0	2 yr	Airway hyperresponsiveness Symptom-free days Morning PEF Evening PEF	FEV ₁	Airway irritation (cough, dyspnea, wheezing, and bronchospasm)	No abnormalities on chest CTs at 1 and 2 yr
Cox and colleagues (AIR trial) (31)	Prospective, randomized, controlled	112	Moderate to severe persistent asthma, ≥ 200 , 0	5 yr	AQLQ scores ACQ scores Symptom-free days Rescue medication use Morning PEF	Rescue medication use Airway hyperresponsiveness FEV ₁	Airway irritation (cough, dyspnea, wheezing, and night awakening) Increase in hospitalization rate	No increase in clinical events or reduction in FEV ₁ at 5 yr as compared to control subjects
Pavord and colleagues (RISA trial) (32)	Prospective, randomized, controlled	32	Severe persistent asthma (refractory asthma), ≥ 1500 , ≤ 30	1 yr	AQLQ scores ACQ scores Rescue medication use Pre-bronchodilator FEV ₁	Morning PEF Evening PEF Symptom-free days Airway hyperresponsiveness Post-bronchodilator FEV ₁ %	Airway irritation (cough, dyspnea, wheezing, discolored sputum, and chest discomfort) Increase in hospitalization rate Lobar or segmental lung collapse	No increase in clinical events or in hospitalization rate up to 1 yr as compared to control subjects
Castro and colleagues (AIR 2) (33)	Randomized, double-blind, sham-controlled	288	Severe persistent asthma, > 1000 , ≤ 10	1 yr	AQLQ scores Severe asthma exacerbations Emergency department visits Days missed from work or school	Morning PEF Symptom-free days Symptom scores ACQ scores Rescue medication use Pre- or post-bronchodilator FEV ₁ %	Airway irritation (cough, wheezing, and chest discomfort) Upper respiratory tract infections Increase in hospitalization rate Rare events (lobar or segmental lung collapse, lower respiratory tract infections, and hemoptysis)	Decrease in clinical events and no change in hospitalization rate up to 1 yr as compared to control subjects

Definition of abbreviations: ACQ = asthma control questionnaire; AIR = asthma intervention research; AQLQ = asthma quality of life questionnaire; FEV₁ = forced expiratory volume at 1 second; ICS = inhaled corticosteroid; OCS = oral corticosteroid; RISA = research in severe asthma; PEF = peak expiratory flow.

*ICS dose of beclomethasone or equivalent.

The definitive study for BT employed a randomized, double-blind, sham-controlled design and enrolled 288 subjects with severe persistent asthma from 30 U.S. and international centers (33). Although a sham arm that exposes subjects to risks with no perceived benefits is controversial, it was necessary given the subjective primary outcome of the study (the Asthma Quality of Life Questionnaire [AQLQ]). The study maintained a double-blind design by having an unblinded bronchoscopy team that performed the procedure and a blinded assessment team that measured blinded patients' responses in the posttreatment period. Patients in this study demonstrated severe asthma as defined by the Severe Asthma Working Group, based on their high requirement for inhaled medications, low AQLQ scores, and low percentage of symptom-free days (34). However, their baseline FEV₁ averaged 77.8–79.7%, a value higher than the proposed FEV₁ of less than 60% in the NAEP guidelines (2). Moreover, patients with a history in the previous year of three or more hospitalizations for asthma exacerbations, three

or more lower respiratory infections, or four or more pulses of oral steroids were excluded from the study, which brings into question the severity of asthma in the studied cohort. Overall, there was a statistically significant improvement in the AQLQ score from baseline values in the BT group compared with the sham group (BT, 1.35 ± 1.10 ; sham, 1.16 ± 1.23); however, this difference in the primary outcome of the study fell below the clinically meaningful change in AQLQ score of 0.5 or greater. In addition, the improvement in AQLQ score in the sham group was greater than expected, possibly due to the placebo effect of bronchoscopy by itself, the enthusiasm for a new technology on the part of enrolled subjects, or simply because of the better medical care that patients usually receive during the course of a clinical trial. Thus, diminished efficacy of the intervention was appreciated when the placebo arm became more invasive. There was no difference between the two groups in morning peak flow, rescue medication use, or FEV₁. The more notable findings of this study were its secondary outcomes, in which BT

subjects experienced a significant reduction in severe exacerbations, emergency department visits, and days missed from work or school in the posttreatment period (6–52 wk post-BT). It is important to note that exacerbations and hospitalizations in the immediate postprocedure period were not included in the secondary outcome analysis. The short-term adverse events were similar to other trials and included airway inflammation and upper respiratory infections. A higher hospitalization rate post-BT was noted (BT, 8.4%; sham, 2%), as well as rare events of lower respiratory infection, segmental or lobar collapse, and one episode of massive hemoptysis (the latter requiring bronchial artery embolization).

Data on the long-term safety of BT are evolving and are currently limited to two reports: the first report combined data from the first three human trials mentioned previously and demonstrated clinical, functional, and radiographic stability over a 3-year period after BT; the second report monitored 45 of the 52 BT subjects enrolled in the AIR Trial and found no increase in the rate of clinical complications or reduction in FEV₁ over a 5-year period post-BT (35, 36).

The persistence of effectiveness of BT at 2 years posttreatment has been documented; 92% of patients in the intervention group in the AIR-2 Trial were evaluated during the second year after BT and found to have the same rate of respiratory events in Year 2 as in Year 1 (asthma exacerbations, respiratory adverse events, emergency department visits, and hospitalization) (37). This follow-up study did not compare outcomes in the sham group, which is necessary to make an accurate assessment of sustained improvement of this intervention. Additional follow-up in BT patients is in progress, as there is a pressing need to continue to evaluate long-term outcomes. There are also studies in progress in which airway biopsy is performed to directly evaluate the airway structural changes associated with thermoplasty (M. Castro, personal communication).

PROCEDURAL ASPECTS

Bronchial thermoplasty is performed in three bronchoscopic sessions, at 2- to 3-week intervals. The first two sessions are typically dedicated to treat each lower lobe separately, while the third session targets both upper lobes. The rationale behind dividing BT into three sessions is the length of time required to treat all visible airways in the intended lobe and the prevention of clinical consequences of widespread irritation of the airways. The airways of the right middle lobe are avoided because of an unproven but time-honored concern about inducing stenosis in the elongated and slender right middle lobe bronchus, otherwise known as the right middle lobe syndrome (38).

Contraindications to BT include the presence of an implantable electronic device, known hypersensitivity to drugs used during bronchoscopy and any severe comorbid conditions that would increase the risk of adverse events.

Patients are usually prescribed a 5-day course of 50 mg of prednisone to begin 2–3 days before the procedure to attenuate airway inflammation after the procedure. On the day of bronchoscopy, all patients should be carefully evaluated for any signs of an active asthma exacerbation or respiratory infection that would be ground for procedure cancellation. Portable spirometry to establish preprocedure baseline and treatment with nebulized bronchodilator before the procedure are recommended. A grounding plate is placed on the patient's torso and connected to the energy controller to complete the electricity circle. Oxygen supplementation during the procedure should be reduced to less than 40% fraction of inspired oxygen to prevent ignition of the airways. A standard adult bronchoscope with a minimal working channel diameter of 2 mm is required.

Bronchoscopy with BT can be done with local anesthesia and moderate sedation or with deep sedation. The procedure begins

with a thorough airway examination to check for any mucosal or secretions characteristic of infection, which should prompt a discontinuation of the procedure. If this is the second or third BT bronchoscopy, the operator should carefully inspect the previously treated airways for any signs of inadequate healing, which would require a rescheduling of the procedure (39). Next, the bronchoscope is navigated to the most distal branch of the targeted airway and stopped at a point that maintains bronchoscopic view of the small airway wall. The catheter is then inserted through the bronchoscope to treat the most distal visible part of the airway. The electrode basket is expanded, via a proximal handle, enough to establish sufficient contact with the airway wall (Figure 2). The energy delivery is initiated via a foot switch and lasts approximately 10 seconds for each application. A distinctive sound generated by the controller accompanies each activation and is disrupted when contact of the electrodes with the airway wall is lost. Once an activation is completed, the operator collapses the electrodes basket and retracts the catheter 5 mm to start the next application. Repeated applications are performed from distal to proximal branches at 5-mm intervals to achieve contiguous nonoverlapping treatment of the entire targeted airway (40). Five-millimeter markings exist on the distal portion of the catheter to assist the operator in following the recommended distance for adjacent applications. It is important for the operator to have a systematic plan to sequentially treat all the distal segmental branches in order not to skip a segment or duplicate a treatment in another segment. Because of variation in airway anatomy among patients, the number of activations required per procedure varies a great deal but averages 40–60 activations, leading to an average length of a BT bronchoscopy of 45–60 minutes (10).

At the end of the procedure, the patient should be carefully monitored in the recovery area and discharged once baseline status is regained and postprocedure FEV₁ is equal to or greater than 80% of preprocedure measurement. The treating physician should maintain close follow-up with the patient in the first week after BT to treat any emergent respiratory ailments. Repeat BT treatments, for patients who underwent three BT treatments but did not sustain the initial benefits, are currently not approved.

CURRENT STATUS OF BRONCHIAL THERMOPLASTY

In April 2010, the U.S. Federal Drug Administration (FDA) approved bronchial thermoplasty for the treatment of severe persistent asthma in patients 18 years and older whose asthma is not well controlled with inhaled corticosteroids and long-acting β -agonists. The FDA has required additional postapproval studies to include a continuation of the AIR-2 Trial with longitudinal data on the durability of effectiveness of BT out to 5 years and a new prospective open-label, single-arm, multicenter study in the United States to demonstrate durability of treatment effect and safety out to 5 years from treatment (http://www.accessdata.fda.gov/cdrh_docs/pdf8/P080032a.pdf).

Bronchial thermoplasty is currently not recognized by governmental and most private insurance parties in the United States, which has limited its clinical adoption. Once this barrier is surmounted, issues of patient selection, and physician training and credentialing, become essential to ensure proper dissemination of a potentially useful technology.

With respect to patient selection, it should be stressed that BT is appropriate only for adult patients with severe persistent asthma that is not controlled with maximal medical treatment. The lower limit of FEV₁ in the largest study (AIR-2) was 60%, and thus lung function should be considered when referring patients for

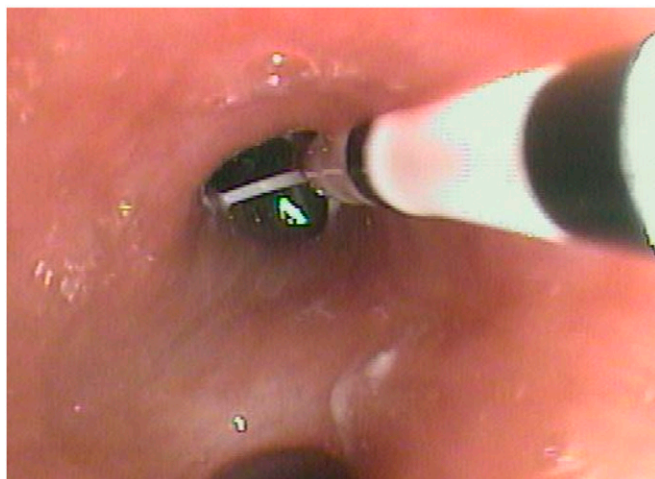
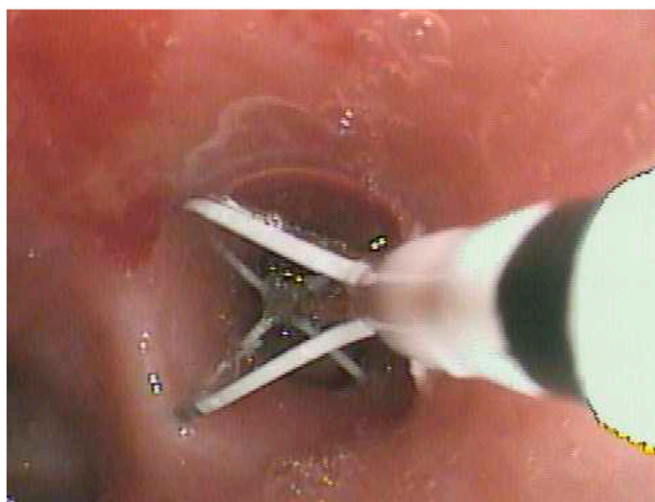
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Figure 2. Bronchial thermoplasty treatment in the airways. (A) Application of thermoplasty in a distal airway; the basket should remain in bronchoscopic view during the application. (B) Application of thermoplasty in a proximal airway; the electrodes are in close contact with the airway wall.

treatment. In addition, BT cannot be a substitute for medical adherence or a life style choice of refusing medicinal treatment.

Issues of physicians' skill acquisition and competency are at the core of every newly approved procedure, particularly for practicing chest physicians who are out of fellowship training. It is clear that BT requires more expertise than an average bronchoscopy because of its intricate technical steps, longer procedural time, sicker patient population, and higher potential for short-term adverse events. The general consensus is that only interventional pulmonologists or bronchoscopists with advanced bronchoscopy skills and high bronchoscopy volumes should perform BT to ensure the best outcome in this labile and fragile patient population. Training can be obtained via structured courses with curricular and practical portions followed by proctored procedures by experienced operators. Simulation, via advanced software technology, has been validated as a tool for training and performance measurement for simple bronchoscopic tasks and can be a valuable adjunct training tool if developed for advanced procedures such as BT (41).

ADVANTAGES AND DISADVANTAGES OF BRONCHIAL THERMOPLASTY

Bronchial thermoplasty presents a new nonmedicinal treatment option for patients with severe asthma who are adherent to a maximal medical regimen and yet suffer from poor control and severe disease. An addition to the armamentarium against such a global and devastating disease is a welcome development. However, cost may be the biggest detriment to the dissemination of this technology, including the cost of three bronchoscopies, the high price of disposable catheters (currently ranging in the thousands of dollars), and variable cost of treatment of postprocedure exacerbation and hospitalization. This is particularly problematic in developing countries, where the need for optimal treatment of severe asthma is sorely needed. Only a well-designed cost-effective analysis will determine whether the cost of this technology can be justified in light of its potential economical benefits. Additional drawbacks are the unknown durability of clinical benefits after treatment and the unknown long-term complications beyond 5 years. Both concerns are currently being addressed in ongoing post-FDA approval studies.

Ultimately, the internal debate in the minds of the treating physician and the patient should weigh the short-term worsening in asthma and the unknown long-term complications against a potential benefit in asthma control and enhancement in quality of life.

FUTURE DIRECTIONS

There is a pressing need to understand the underlying mechanism of BT and how its delivered heat is translated into clinical benefit. Ongoing and future studies should attempt to obtain endobronchial biopsies from treated areas with close examination of alterations in anatomical structures and inflammatory markers. Prior histological data of BT effects on the airways had come from animal models or subjects who did not carry the diagnosis of asthma (9).

Clinical trials on BT demonstrated that a favorable clinical response was not uniform among patients with asthma. This necessitates additional investigation to identify disease and patient characteristics that would enable accurate phenotyping of positive responders to avoid unnecessary procedures and risks.

Finally, bronchial thermoplasty in its current form is somewhat tedious, taxing on the patient, and expensive. Therefore, the ability to deliver biological agents, systemically or via inhalation, which can disrupt the function of the ASM would be an attractive strategy that reaches proximal and distal airways and is delivered in a less invasive fashion.

CONCLUSIONS

Bronchial thermoplasty is a novel treatment for patients with severe asthma who remain symptomatic despite adherence to the standards of medical care. Data from clinical trials suggest that patients treated with BT may experience an improvement in quality of life and reduction in the rate of severe exacerbation, emergency department visits, and days lost from school or work. The generalizability of these findings to all patients with severe asthma is not clear, given the exclusion of patients with severe asthma who exacerbate frequently, require multiple bursts of oral corticosteroids, and demonstrate low lung function.

The short-term adverse events consist primarily of airway inflammation and occasional more severe events requiring hospitalization. Proper patient selection and optimal pre- and post-procedural management are essential for a successful outcome. Further studies are needed to determine the durability of clinical effects, assess long-term adverse events, and further understand the mechanism of BT on asthma pathobiology.

Author disclosures are available with the text of this article at www.atsjournals.org.

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