Chapter

Bronchial Thermoplasty: A New Therapeutic Option in Severe Uncontrolled Asthma

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Abstract

Bronchial thermoplasty (BT) is a new endoscopic treatment approved by the US Food and Drug Administration (FDA) in the management of severe refractory asthma involving the delivery of controlled, therapeutic radiofrequency (RF) energy to the airway wall. It is based on the premise of controlling bronchospasm through a reduction of airway smooth muscle (ASM). Several clinical trials have demonstrated improvements in asthma-related quality of life and a reduction in the number of exacerbations following treatment with BT. However, several questions remain regarding the use of BT, mechanism of action, selection of appropriate patients, and long-term effects. Further studies are expected to elucidate the underlying mechanisms that result in these improvements. This chapter discusses key aspects of BT with a focus on the potential clinical effects of this promising procedure. It also offers insight into the barriers to implementing a successful BT program and strategies for overcoming them.

Keywords: severe asthma, bronchial thermoplasty, bronchoscopy, airway smooth muscle

1. Introduction

Asthma is a common condition affecting more than 235 million people worldwide [1]. Asthma is a chronic inflammatory disease characterized by variable airflow obstruction and bronchial hyperreactivity associated with airway remodeling. Clinically, this manifests as recurrent episodes of wheezing, cough, dyspnea, and chest tightness. Asthma treatment as of current standard is based on reducing inflammation with inhaled corticosteroids (ICS) and relaxing airway smooth muscle (ASM) with inhaled bronchodilators along with minimizing exposure to allergic triggers [2]. While most patients achieve symptom control with these strategies, there remains a significant cohort with severe asthma estimated at 5–10% who are more difficult to treat. This group of severe asthmatics, however, is responsible for a disproportionate share of the morbidity associated with the disease. The severe asthma group is responsible for most of the asthma-related healthcare burden, represented by the costs of hospitalizations, ER visits, physician office visits, and use of medications [3–5]. This increased burden of severe asthma reflects the inability of the existing treatment options to adequately control asthma in patients with severe disease.

Severe Asthma is defined by the American Thoracic Society and European Respiratory Society as asthma requiring treatment with high-dose ICS and a second controller medication (and/or systemic corticosteroids) to maintain asthma control [6]. Unfortunately, therapeutic options for patients with severe asthma are limited. Biologic therapy targeting IgE, IL-4 and IL-5 have been of particular interest recently. In the past decade, new therapeutic approaches for asthma have included the use of biological agents, such as omalizumab, a recombinant DNA-derived humanized monoclonal antibody to IgE. However, in patients with severe asthma with no indication for or those lacking a response to omalizumab, the new targeted anti-IL-5 monoclonal antibodies including mepolizumab and reslizumab, have been recently approved [7, 8]. However, they only appear effective in certain subgroups of patients with asthma. Hence, new treatment strategies and approaches are urgently needed for these patients. BT is a novel nonpharmacological therapy which targets ASM in an effort to improve asthma control.

2. Airway smooth muscle in asthma

The airway smooth muscle (ASM) plays significant role in multiple normal processes in the healthy airway, including control of bronchomotor tone, immunomodulation, and extracellular matrix deposition. ASM cells in asthma patients proliferate more rapidly than in non-asthmatic patients, resulting in an increase in smooth muscle mass, with airway narrowing and loss of respiratory function [9]. As a result, the proliferation and differentiation of mesenchymal cells to myofibroblasts increases the deposition of extracellular matrix (ECM) and smooth muscle cells [10]. All of the above modifications, in particular, ASM and ECM deposition, increase the airway wall thickness, which correlates with severity and duration of clinical episodes of asthma [11]. Bronchial remodeling, an increase in ASM, has been shown to be related to clinical and functional severity of asthma [9]. It has been shown that those with fatal asthma have an increased volume of smooth muscle compared with nonfatal asthma [12].

These published findings led to the conclusion that smooth muscle cell alteration is the fundamental structural change that distinguishes severe from moderate asthma, and that phenotypic changes in ASM could contribute to reducing control in subjects with severe asthma [13]. As a result, ASM has become a therapeutic target.

3. Bronchial thermoplasty

BT is a nonpharmacological, novel endoscopic therapy that delivers controlled RF thermal energy to the airway wall as part of a series of three bronchoscopic procedures. It was approved by the US Food and Drug Administration for the treatment of severe persistent asthma in patients aged over 18 years in 2010.It involves application of RF thermal energy to the airways in asthma patients with the goal of ablating the ASM. The first study of BT in human airways involved subjects undergoing lobectomy for known or suspected lung cancer [14].

The current understanding is that BT can denature and destroy ASM and allows the reduction of bronchospasm which in turn results in improved control of the symptoms of severe asthma. Previous canine animal models have demonstrated that BT causes almost complete destruction of ASM with moderate connective tissue deposition when lung tissue has been examined histologically [15].

Several clinical trials have demonstrated the long-term safety and effectiveness of BT in terms of reducing exacerbations of asthma and improving patient quality of life [16].

This chapter will summarize the information on mechanism of action, procedure, efficacy, safety and patient selection, to better understand the path forward for this promising technique.

4. Efficacy data in the short and long term: BT trials to real life

The first randomized clinical trial (RCT) evaluating the efficacy of BT was conducted in 2006 by Cox et al. on 16 patients with stable mild-to-moderate asthma [17]. In general, BT was well tolerated, with most of the procedure-related adverse events occurring in the week following the procedure. Most of the events were mild and transient and resolved spontaneously or required minor changes in medications. There was a significant reduction in airway hyperresponsiveness as reflected by increased PC20 (provocative concentration causing a 20% decline in FEV1). In addition, there was a significant improvement in symptom-free days (47 vs. 73%, $P = 0.015$) and peak expiratory flow rates measured at 12 weeks following BT. Interestingly, there was no change in FEV1 during the 2 years of follow-up. Chest CT was performed at 1 year and 2 years following BT did not reveal any bronchiectasis or parenchymal lung disease [17].

Asthma Intervention Research (AIR) trial was the next major RCT in 2007. AIR included 112 patients with moderate-to-severe asthma (FEV1 between 60 and 85% of predicted) treated with BT [18]. Although, there were no differences in prebronchodilator FEV1 percentage of predicted (72–74.3% vs. 75.8–75.7%, $P = 0.28$) between patients who underwent BT and the control group when compared to their pre-randomization baseline. There was, however, a significant improvement in asthma symptoms as reflected by symptom-free days ($40.6 \pm 39.7\%$ vs. $17.0 \pm 37.9\%$, $P = 0.005$), scores of the asthma control questionnaire (ACQ) (reduction, 1.2 ± 1.0 vs. 0.5 ± 1.0, $P = 0.001$) and asthma quality of life questionnaire (AQLQ) (1.3 ± 1.0 vs. 0.6 ± 1.1, $P = 0.003$). Moreover, there was a significant reduction in mild exacerbations of asthma and an increase in the morning PEF, in patients treated with BT [18].

In 2007, the Research in Severe Asthma (RISA) designed to evaluate the safety and efficacy of BT in patients with severe, symptomatic asthma was published [19]. This smaller trial included 32 patients (15 randomized to BT) with severe persistent asthma as defined by uncontrolled symptoms despite high-dose ICS and LABA use. Patients in BT arm showed a significant improvement in pre-bronchodilator FEV1. The improvements in ACQ and AQLQ score persisted despite the reduction of OCSs and bronchodilators.

These results were promising, however questions remained over the true efficacy of BT versus potential placebo effect as the RISA and the AIR trials were unblinded [19]. The AIR-2 trial was designed to answer these questions.

5. AIR-2 trial

The largest RCT, AIR2, was a double-blinded, randomized, sham-controlled study included patients who had uncontrolled asthma despite high-dose ICS and a LABA [20]. A total of 190 patients were treated with BT and 98 control patients received sham thermoplasty. The procedure was performed by an unblinded bronchoscopy team and all the assessments and follow-up visits were conducted by

Study	Study population	Study design	Results
Cox et al. [17]	16 patients with mild-to-moderate stable asthma	Non-randomized, prospective study	Significant reduction in airway hyperresponsiveness and increase of symptoms-free days. No changes in FEV1
Cox et al. [18]	112 patients with moderate-to-severe asthma	Randomized, controlled trial	Improvements of asthma symptoms, symptom-free days, and AQLQ and ACQ scores, and reduction in mild exacerbations. No changes in FEV1 and bronchial hyperreactivity
Pavord et al. [19]	32 patients with severe uncontrolled asthma	Randomized, double-blind, parallel-group trial	Significant improvement in FEV1 and ACQ scores. Limitation: effective placebo
Castro et al. [20]	288 patients with severe, uncontrolled asthma	Randomized, double-blind, controlled, multicenter-based trial	Increase of AQLQ score, and reduction of rate of exacerbations, emergency hospital visits, and lost working days
Thomson et al. [21]	69 patients enrolled in the AIR trial	Long-term follow-up study	Significant reduction in airway hyperreactivity and stability of FEV1. No radiological changes
Pavord et al. [22]	14 patients enrolled in RISA trial	Long-term follow-up study	Significant decrease of emergency hospital admissions. No changes of FEV1 value
Wechsler et al. [23]	160 patients enrolled in AIR-2 trial	Long-term follow-up study	Significant decrease of emergency hospital admissions

Abbreviations: FEV1, forced expiratory volume in 1 sec; AQLQ, Asthma Quality of Life Questionnaire; ACQ, Asthma Control Questionnaire; AIR, Asthma Intervention Research; RISA, Research in Severe Asthma.

Table 1.
Summary of clinical trials and long term follow up with BT in asthma.

a blinded team [20]. The primary outcome measure was to evaluate change from baseline in average group mean Asthma Quality of Life Questionnaire (AQLQ) score. In the BT group, a significantly greater proportion had a significant increase in the AQLQ score compared with those who underwent sham bronchoscopy (79 vs. 64%). There was also a meaningful reduction in the number of exacerbations (32% risk reduction), emergency department visits (84% risk reduction) and days lost from school/work (66% risk reduction) in those in the BT arm [20].

The results of these large RCTs are summarized in **Table 1**.

6. Long-term follow up and safety of BT

The earlier large clinical trials of BT showed marked improvements in asthma-related quality of life and a reduction in the number of exacerbations and led to the approval of the use of BT by the FDA in 2010 (**Table 1**). However, long-term safety of BT was largely unaddressed, especially because of early concerns about thermal tissue damage, possible subsequent risk of bronchial stenosis, and bronchomalacia remained to be investigated. Recently, the results from the long-term follow-up of patients enrolled in the AIR, RISA, and AIR-2 trials have provided some clarity in this regard.

From the original study population of patients in the AIR trial, 45 patients treated with BT and 24 control patients were followed for an additional 4 years

(5 years in total) and an additional 2 years (3 years in total) respectively [21]. In comparison to the control subjects, patients who underwent BT had similar rates of adverse respiratory events, oral corticosteroid bursts requirements, hospitalizations, and emergency department visits. Further, patients treated with BT continued to show improvements in airway hyperresponsiveness lasting up to 3 years, suggesting the long-term efficacy of the procedure [21].

A long-term follow up of the patients with BT included in the RISA study, performed for a total of 5 years, showed a significant decline in emergency visits and hospitalizations for an exacerbation of asthma, and no further deterioration of FEV1 [22].

Similarly, in the AIR-2 follow up study, patients were also monitored for another 4 years to evaluate the long-term effects of BT [23]. Patients treated with BT showed a definite decrease in severe exacerbations of asthma and emergency hospital visits [23]. Interestingly, a recent large retrospective study of patients with persistent asthma suggests constant exacerbation frequency despite continued high-intensity therapy with high doses of ICS and LABAs [24]. Therefore, long-term comparative head to head safety studies for the use of BT in the treatment of asthma are nevertheless required in future also.

7. Patient selection for bronchial thermoplasty

Currently, BT is approved for patients with uncontrolled severe persistent asthma despite the use of an inhaled corticosteroid and LABA. As per the recent Global Initiative for Asthma (GINA) guidelines, it has been suggested that "for highly-selected adult patients with uncontrolled asthma despite use of recommended therapeutic regimens and referral to an asthma specialty center, BT is a potential treatment option" (Grade B evidence) [25]. In general, BT remains contraindicated in patients with a pacemaker, internal defibrillator, or any implantable electronic device [25].

Prior to consideration of BT, patients should undergo a focused evaluation to ensure that the diagnosis of severe asthma is correct, treatment is optimized, and comorbid conditions are treated. A thorough history and detailed physical examination constitute the next step. In addition, workup as necessary to exclude an alternative diagnosis, such as sarcoidosis, cystic fibrosis (CF), other non-CF bronchiectatic lung disease, alpha-1 antitrypsin deficiency, and chronic obstructive pulmonary disease (COPD) should also be carried out [26]. In general, full pulmonary function testing as well as a high-resolution CT scan of the lungs is also desirable. Before labeling it as severe asthma, the inhaler technique and adherence are also evaluated rigorously, as corrective interventions have shown to improve asthma control [27].

8. BT procedure

BT is based on the principle of endobronchial controlled delivery of RF thermal energy to modify the structure of the airway wall thereby reducing the amount of ASM with a device called the Alair BT System (Boston Scientific, Marlborough, MA, USA). A bronchoscope with a disposable catheter with a diameter of 2.0 mm in the operating channel is used to obtain better visualization and complete treatment of subsegmental bronchi [17]. The distal tip of the catheter has an expandable four-electrode basket, through which 65°C radio frequencies are delivered in order to visible bronchial areas sequentially [17]. The correct order involves the right lower

lobe (first session) then left lower lobe (second session), followed by both upper lobes (third session). The right middle lobe is generally not treated because of the remote possibility of obstruction and right middle lobe syndrome. A typical BT session lasts about 30–45 min.

The entire visible length of each bronchus is treated with each pulse targeting a 5 mm section of bronchus between 3 and 10 mm in diameter, starting at the periphery and moving proximally. On an average the full treatment consists of 30–70 activations per lobe, up to 44 for the right lower lobe, 47 for the left lower lobe and 60 for the upper lobes [21]. Successful BT comprises three procedures performed at 20 day intervals [17]. Mild bronchoconstriction, mucous hypersecretion, and minor bleeding related to superficial trauma are the most commonly encountered complications. Patients are given systemic corticosteroids and nebulized. Bronchodilators prior and after the procedure to minimize the complications in the post procedure setting.

BT should be performed by an experienced bronchoscopist in an adequate setting with appropriate clinical monitoring and the facility and expertise to address any potential post-intervention complications. Mayse et al. has described the appropriate assessment and monitoring of the patient before, during and after the procedure [28].

9. What are the current guidelines regarding bronchial thermoplasty?

As per the current European Respiratory Society and American Thoracic Society (ERS/ATS) guidelines BT is recommended in adults with severe refractory asthma, despite optimal therapy, in the context of an institutional review board-approved independent systematic registry, or for use in a clinical study only [29]. A recent Cochrane Database systematic review also has the same recommendation and highlights the need for further studies on BT to determine the mechanisms of action in patients with different phenotypes of asthma [30]. Interestingly the BT Global Registry, a 2 year observational study is expected to provide new and valuable data on BT, is currently recruiting patients [31].

10. Pharmacoeconomics of bronchial thermoplasty

BT is an expensive procedure, but recent studies have shown that the obvious high cost may be at least partially balanced by the reduction in costs due to decrease in acute exacerbations of asthma requiring emergency department visits and the effects of improved quality of life for patients [32]. A subsequent study has confirmed that BT has a 60% chance to be more cost effective as compared with omalizumab and standard therapy on the willingness-to pay of $100,000/quality-adjusted life year [33]. Zein and colleagues also concluded that BT is a cost effective intervention in patients with asthma at high risk of exacerbations [34]. However, a study carried out in Singapore found that BT is not cost effective compared with optimized asthma therapy unless the cost of the procedure is decreased so as to make it more cost effective [35].

11. Conclusions

BT is the only FDA approved nonpharmacological treatment available for severe asthma patients. In contrast to therapies for asthma targeting the underlying

inflammatory response, BT specifically targets the ASM. Recent clinical trials have established its safety, ability to improve quality of life and reduction in exacerbations in patients with severe asthma. However, the exact mechanisms that underlie these improvements seen with BT remain at best still poorly understood. Future studies on the mechanism of action of BT, including phenotyping of patients and treatment approaches in identifying the patients most likely to respond to this therapy are expected to solve the existing conundrum.

Conflict of interest

The author does not disclose any conflict of interest.

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