

Critical Review of Bronchial Thermoplasty: Where Should It Fit into Asthma Therapy?

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Abstract Bronchial thermoplasty is a device-based therapy for treatment of severe refractory asthma that uses radiofrequency energy to reduce airway smooth muscle and decrease bronchoconstriction. BT improves quality of life and decreases the rate of severe exacerbations with no known major long-term complications. The effectiveness of bronchial thermoplasty persists at least 5 years after the treatment is completed. Further investigation is needed to better define the specific subpopulation of patients with severe asthma who would best benefit from this treatment.

Keywords Bronchial thermoplasty · Severe asthma · Quality of life · Airway smooth muscle · Targeted therapy

Introduction

Asthma continues to be an increasingly prevalent worldwide health problem, affecting over 235 million people globally and 25 million people in the USA [1, 2]. Health care costs attributed to asthma exceed US\$56 billion annually in the USA, and despite representing the minority of patients with asthma, those with severe asthma account for the lion's share

(estimated at 80 %) of this economic burden [3, 4]. Patients with severe asthma have a greater burden of symptoms at baseline and have more frequent, severe exacerbations [5]. In addition, the majority of health care costs associated with severe asthma are due to hospitalizations or emergency department visits [6]. Prevention of exacerbations and better control of symptoms can potentially minimize the substantial expenditure associated with severe asthma.

The American Thoracic Society and European Respiratory Society defines severe asthma as asthma which requires treatment with high-dose inhaled corticosteroids (ICS) plus a second controller and/or systemic corticosteroids for ≥ 50 % of the previous year to prevent it from becoming “uncontrolled” or that remains uncontrolled despite this therapy [7]. Though patients with severe refractory asthma constitute a heterogeneous population [8], they share a common need for new therapies and strategies to achieve adequate control of their symptoms. Despite new insights into the pathobiology of asthma, few therapies have emerged in the past decade that substantially changed the treatment of severe asthma. ICS and β_2 -agonists have been the mainstays of asthma therapy for many years, and further discussion of these agents is beyond the scope of this review [9, 10]. Adding a leukotriene receptor antagonist (LTRA) to an ICS regimen is no better than increasing the dose of ICS [11], and there are no conclusive studies of the efficacy of LTRA in severe asthma. The 5-lipoxygenase inhibitor zileuton improved lung function and asthma control in placebo-controlled studies of mild-moderate asthma [12, 13], and post hoc data suggest that these improvements translate to patients with severe asthma with a forced expiratory volume at 1 s (FEV_1) ≤ 50 % [14]. However, enthusiasm for zileuton is limited by a high monthly cost and concern for hepatic toxicity with a need for frequent laboratory monitoring. The anti-IgE recombinant monoclonal antibody omalizumab is effective as an add-on therapy to high-dose ICS regimens in asthmatic patients with sensitivity

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to aeroallergens [15, 16], but its utility is limited by inconclusive efficacy in non-atopic asthma [17], high cost [18], and the need for long-term administration to maintain efficacy. With further insight into the complexity of severe refractory asthma, targeted therapies will become available that can potentially change the landscape of asthma treatment [19].

Airway Smooth Muscle as a Therapeutic Target in Severe Asthma

Though the majority of therapies in development target inflammatory pathways in asthma, airway smooth muscle is a modifiable structural target and is one of the key components of bronchoconstriction and increased airway resistance in asthma. Airway smooth muscle cells undergo hypertrophy in asthma and hyperplasia in fatal asthma [20]. Early studies by James and others found that smooth muscle hypertrophy altered the mechanics of airway narrowing such that the same degree of muscle shortening in asthma increased resistance nearly 20 times more than in normal airways [21]. This exaggerated narrowing was magnified by airway wall thickening, which is more pronounced in severe asthma [22]. Airway smooth muscle cells are also active in immunomodulation and can contribute to both angiogenesis and extracellular matrix formation, though these roles have not been clearly defined [23]. The reduction of airway smooth muscle mass is an intriguing strategy in improving airway resistance in asthma.

Indeed, Danek et al. theorized that airway smooth muscle could be ablated by the administration of thermal energy from a radiofrequency (RF) source [24]. The investigators delivered low-dose thermal energy through a four-electrode basket catheter conveyed through the working channel of a bronchoscope. Though the airways blanched on immediate administration of heat, this blanching and erythema had mostly resolved by 1 week, and no long-term adverse effects were noted. Their study found that the application of low-dose thermal energy to canine airways decreased smooth muscle mass and airway responsiveness to methacholine. The reduction in airway responsiveness correlated well with the degree of reduction of smooth muscle in the airway wall, and the effects were seen within 1 week and persisted up to 3 years. In addition, when compared to untreated canine airways, high-resolution computed tomography of canine airways treated with thermal energy demonstrated increased airway distensibility at 3 weeks at a wide range of airway pressures [25]. The canine airways also showed a decreased bronchomotor tone both at baseline and in response to increasing doses of methacholine 2 weeks after treatment [26]. These preclinical data suggested that decreasing smooth muscle may decrease airway hyperresponsiveness in humans, potentially limiting airflow obstruction in response to provocative stimuli. Since

radiofrequency-generated thermal energy has been used in higher amounts in a variety of clinical scenarios with acceptable safety parameters, the natural next step was to translate this new technology to humans with severe asthma. The delivery of thermal energy from a radiofrequency source via bronchoscope to airways to decrease smooth muscle mass has been referred to as “bronchial thermoplasty.”

Overview of the Bronchial Thermoplasty Procedure

Bronchial thermoplasty is performed in humans using the Alair Bronchial Thermoplasty System (Fig. 1) (Boston Scientific, Inc., Natick, MA) which includes the Alair RF controller and Alair RF catheter (Fig. 2). The RF catheter is a flexible, disposable catheter that inserts through the working channel of a normal bronchoscope (outer diameter, 4.9–5.2 mm) and has an expandable four-arm array at the distal tip. These arms are designed to fit into airways 3–10 mm in diameter and can be expanded using a depressible actuator on the handle attached to the catheter. The proximal end of the catheter attaches to the RF controller, which in turn is connected to a depressible footswitch used to initiate the delivery of RF-generated thermal energy. When the footswitch is depressed, the controller system delivers an appropriate amount of thermal energy (maximum 120 J) to an airway. Lastly, a return electrode is placed on the patient's back or thigh and connects to the RF controller, completing the circuit.

The U.S. Food and Drug Administration approved bronchial thermoplasty in 2010 for use in patients over the age of 18 who have incomplete control of asthma despite the regular use of ICS and long-acting β_2 -agonist (LABA) medications. Exclusion criteria include the presence of a pacemaker, defibrillator, or other implantable electronics; sensitivity to typical medications used during bronchoscopy (lidocaine, atropine, benzodiazepines); history of smoking within the past year or significant prior history of smoking (greater than 10 pack-years); active respiratory infection or asthma exacerbation within the 2 weeks prior to treatment; or known coagulopathy (Alair Package Insert). Bronchial thermoplasty is performed



Fig. 1 The Alair controller system



Fig. 2 The Alair catheter with expandable four-arm array. *Black markings* are measured at 5-mm intervals from the tip

in three separate treatments separated by at least 3 weeks. The first treatment involves the right lower lobe, the second involves the left lower lobe, and the final treatment involves both upper lobes. The right middle lobe is not treated due to concerns that it may be more prone to injury [27]. Patients are treated with prednisone at 50 mg/day for 5 days beginning 3 days prior to thermoplasty. Prior to commencing thermoplasty, postbronchodilator FEV₁ should be within 10 % of a previously documented baseline value, and oxygen saturation should exceed 90 %.

Bronchial thermoplasty should always be performed by an experienced bronchoscopist. Prior to the procedure, patients should receive albuterol or a similar short-acting β 2-agonist (albuterol 2.5–5.0 mg via nebulizer or metered-dose inhaler four to eight puffs). An antisialagogue (0.4–0.6 mg IV/IM atropine or 0.2–0.4 mg IV/IM glycopyrrolate) is typically used to minimize secretions during the procedure. Bronchial thermoplasty can be performed either with moderate sedation with a fast-acting benzodiazepine and opioid or under general anesthesia, depending on the preference of the bronchoscopist and institution. Similarly, airway management varies greatly depending on bronchoscopist and institutional practice. The length of the procedure is typically 45–60 min and often dictates choice of sedation and airway management. Topical sedation with 1 % lidocaine is important to minimize cough and should be used generously up to 600 mg or 9 mg/kg [28].

Each treatment begins with a visual inspection of the airway tree in the lobe(s) scheduled to be treated. In addition, previously treated areas are inspected again during subsequent treatments to ensure there is no residual inflammation, scarring, or excessive mucous production. Airways are treated with thermal energy in a methodical fashion, with distal airways typically treated first, as these are the most difficult to treat if airways become inflamed during the procedure. Large lobar segmental airways are typically the last airways to be treated during a session. The bronchoscopist advances the RF catheter tip until it is barely visible at the distal end of the airway. The four-arm array is then expanded and the footswitch depressed, signaling the RF controller to deliver an appropriate amount of thermal energy to the airway. The

catheter is then retracted 5 mm at a time (as indicated by markings on the catheter) so that treatments are adjacent but not overlapping, and the procedure continues until all visible airways in the designated lobe are treated with thermal energy. After the procedure, patients are given short-acting β 2-agonists and monitored until their postbronchodilator FEV₁ is at least 80 % of the preprocedure value. Most patients exhibit increased symptoms (cough, wheeze, chest tightness) 24–72 h posttreatment, but these typically resolve within a week. Criteria for hospital admission include persistently diminished lung function, oxygen saturation <90 %, persistent tachycardia >130 bpm or unstable blood pressure, significant hemoptysis (greater than 50 cc over 4 h), or altered mental status. Patients discharged postprocedure should be followed by telephone at 24 h, 48 h, and 1 week posttreatment and should be seen in clinic prior to the subsequent treatment.

Human Studies of Bronchial Thermoplasty

Table 1 lists a summary of all clinical trials of bronchial thermoplasty that have been published to date. Miller et al. performed the first human bronchial thermoplasties on normal-appearing airways of non-asthmatic patients with lung cancer up to 3 weeks prior to scheduled lung resection [29]. This study confirmed that bronchial thermoplasty decreased airway smooth muscle on histologic sections from the resected lungs, though these patients did not have asthma. In addition, subjects tolerated the procedure well, and any airway inflammation visualized during the procedure had largely resolved by the time of lung resection.

Cox et al. conducted the first non-randomized feasibility study of bronchial thermoplasty in 16 patients with stable asthma who had a low use of short-acting β 2-agonist therapy and a minimal history of lower respiratory tract infections [30]. These subjects had normal lung function (mean prebronchodilator FEV₁ 82 %) but exhibited substantial airway hyperresponsiveness (mean methacholine PC₂₀ 0.92 mg/ml), and most subjects were not on high-dose ICS or an ICS/LABA combination. After bronchial thermoplasty was completed, mean PC₂₀ increased to 4.75 mg/ml at 12 weeks and 5.45 mg/ml at 1 year and remained higher than pretreatment values at 2 years (3.40 mg/ml). Lung function did not change posttreatment, but mean symptom-free days increased from 50 to 73 % postprocedure, with 2/3 of subjects experiencing improvements. Side effects of the procedure were mild and had resolved within 5 days posttreatment, and no severe adverse events occurred.

The Asthma Intervention Research (AIR) trial was the first randomized, controlled trial of bronchial thermoplasty and was designed to investigate improvements in quality of life and frequency of exacerbations after thermoplasty [31]. One hundred twelve subjects aged 18–65 with moderate or severe

Table 1 Summary of clinical trials of bronchial thermoplasty

Study	Primary author	Year	Number of patients	Inclusion criteria	Exclusion criteria	Measured outcomes	Key findings
Feasibility study in non-asthmatic subjects	Miller et al.	2005	9	Subjects with suspected or proven lung cancer scheduled for lung resection		Safety; airway smooth muscle in treated, resected lung. No prespecified primary outcome.	No serious adverse events; decrease in airway smooth muscle
Feasibility study in asthmatic subjects	Cox et al.	2006	16	≥18 years old; mild to moderate, stable asthma	Recent respiratory tract infection, LRTI requiring antibiotics; frequent use of rescue medication	Safety; methacholine PC ₂₀ 2 years post-BT. No prespecified primary outcome.	No severe adverse events; mean PC ₂₀ increased post-BT; increase in symptom-free days in 2/3 of subjects
AIR trial	Cox et al.	2007	112	18–65-year-olds with moderate to severe asthma on high-dose ICS/LABA	Recent LRTI requiring antibiotics; recent respiratory tract infection	Primary: rate of mild exacerbations; secondary: ACQ/AQLQ and asthma symptoms	Decrease in mild exacerbations; improvements in ACQ/AQLQ scores; increased symptom-free days
RISA trial	Pavord et al.	2007	34	18–65-year-olds on high-dose ICS/LABA with airway hyperresponsiveness and uncontrolled asthma symptoms		Primary: safety; secondary: ACQ/AQLQ, FEV ₁ , inhaled and oral corticosteroid dose	BT tolerated well in severe asthma; increase in pre-BD FEV ₁ and ACQ/AQLQ post-BT; increased OCS weaning post-BT
AIR2 trial	Castro et al.	2008	297	18–65-year-olds on high-dose ICS/LABA	Life-threatening asthma; chronic sinus disease; emphysema; recent respiratory tract infection or asthma-related hospitalizations	Primary: change in AQLQ; secondary: severe exacerbations, health care utilization	Higher increase in AQLQ in BT vs. sham; decrease in severe exacerbations and ED visits post-BT
RISA 5 year	Pavord et al.	2013	14	18–65-year-olds on high-dose ICS/LABA with airway hyperresponsiveness and uncontrolled asthma symptoms		Safety; severe exacerbations; lung function	Decrease in ED visits and hospitalizations; maintained increase in FEV ₁ post-BT
AIR2 5 year	Wechsler et al.	2013	162	18–65-year-olds on high-dose ICS/LABA	Life-threatening asthma; chronic sinus disease; emphysema; recent respiratory tract infection or asthma-related hospitalizations	Safety; asthma control; severe exacerbations and ED visits	Persistent decrease in severe exacerbations, ED visits, and hospitalizations post-BT

ACQ Asthma Control Questionnaire, AIR Asthma Intervention Research, AQLQ Asthma Quality of Life Questionnaire, BD bronchodilator, BT bronchial thermoplasty, ED emergency department, FEV₁ forced expiratory volume at 1 s, ICS inhaled corticosteroid, LABA long-acting β_2 -agonist, LRTI lower respiratory tract infection, RISA Research in Severe Asthma, OCS oral corticosteroid, PC₂₀ methacholine challenge, PEF peak expiratory flow

persistent asthma on both high-dose ICS and LABA medications were randomized to either bronchial thermoplasty in addition to ICS/LABA therapy or ICS/LABA therapy alone. The pre-specified primary outcome was the difference between the two groups in the rate of mild exacerbations. Subjects had prebronchodilator FEV₁ between 60 and 85 % predicted, PC₂₀<8 mg/ml, and stable symptoms 6 weeks prior to enrollment. In addition, subjects had to demonstrate worsening asthma control after withdrawing LABA therapy for 2 weeks as noted by either an increase of 0.5 in the Asthma Control Questionnaire (ACQ) [32] or decline in peak expiratory flow (PEF) by 5 %. Subjects who received bronchial thermoplasty had 50 % fewer mild exacerbations at 12 months, as compared to no change for those on conventional therapy. In addition, fewer severe exacerbations occurred in subjects who received bronchial thermoplasty, though this finding did not meet statistical significance. Subjects who received bronchial thermoplasty had more adverse respiratory events immediately after the procedure, and six hospitalizations occurred among four subjects in the thermoplasty group. By 6 weeks, there were no differences in asthma symptoms, and at 12 months, subjects who received bronchial thermoplasty had greater improvements in asthma-specific quality of life as measured by the Asthma Quality of Life Questionnaire (AQLQ) [33], ACQ scores, morning PEF, and symptom-free days as compared to conventional therapy. One major criticism of this study is the lack of a sham control group to account for a possible placebo effect.

The Research in Severe Asthma (RISA) [34] trial was designed to investigate the safety and efficacy of bronchial thermoplasty in severe asthma [34]. Thirty-four subjects aged 18–65 on high-dose ICS and LABA therapy and prebronchodilator FEV₁≥50 % predicted with documented airway hyperresponsiveness and uncontrolled asthma symptoms were randomized to either bronchial thermoplasty or conventional therapy. The pre-specified primary outcome was the number of adverse events in the two groups. Subjects then underwent a standardized weaning protocol of either oral corticosteroids or ICS therapy over 1 year. As with AIR, the RISA trial confirmed an increase in asthma symptoms and risk for hospitalization immediately after treatment with bronchial thermoplasty. In addition, two subjects in the intervention group had lobar collapse in the treated lobe that required treatment. Posttreatment adverse events were similar between the groups, though one subject accounted for all the hospitalizations in the control group. After bronchial thermoplasty, subjects had 15 % higher prebronchodilator FEV₁ and improvements in both AQLQ and ACQ that were not seen in those receiving conventional therapy. Rescue medication use was lower in subjects receiving bronchial thermoplasty, and more subjects were able to wean off oral corticosteroids.

The pivotal AIR2 trial was the first to randomize subjects with severe asthma to either treatment with bronchial

thermoplasty or a sham procedure to minimize potential placebo effects related to receiving thermoplasty and was designed to investigate improvement in quality of life and exacerbation rates after bronchial thermoplasty [35]. Two hundred ninety-seven symptomatic subjects aged 18–65 on high-dose ICS and LABA with oral corticosteroid use <10 mg/day, documented airway hyperresponsiveness, and prebronchodilator FEV₁≥60 % predicted were randomized to either bronchial thermoplasty or a sham procedure in which every step of an actual thermoplasty procedure took place except the delivery of thermal energy. The pre-specified primary outcome was the difference between the two groups in change in AQLQ (average of 6-, 9-, and 12-month post-treatment scores). Though the majority of subjects in both groups experienced an improvement in AQLQ scores after either thermoplasty or sham treatment, more subjects in the thermoplasty group had an improvement greater than the minimally important difference (MID) of 0.5 (79 vs. 64 %). Subjects receiving thermoplasty had 32 % fewer severe exacerbations, fewer days from work or school lost to asthma symptoms, 84 % fewer emergency department visits, and fewer hospitalizations than those receiving sham treatment. Though the difference in improvement of AQLQ scores between thermoplasty and sham groups was less than the MID (0.5 units) of the AQLQ instrument (mean improvement thermoplasty vs. sham, 1.35 vs 1.16), Juniper et al. note that the MID of the AQLQ instrument reflects within-group changes but cannot meaningfully be applied to detect between-group differences [36]. Similar to the AIR and RISA trials, the patients did experience an increase in their asthma symptoms usually within 24–48 h after the treatment and it resolved within a week. The risk of hospitalization was approximately 3 % per treatment. The AIR2 trial highlights the efficacy of bronchial thermoplasty in improving asthma-specific quality of life and decreasing severe exacerbations.

Long-Term Safety of Bronchial Thermoplasty

These trials captured long-term safety data in subjects undergoing bronchial thermoplasty. In the RISA study, 14 of 15 subjects who underwent thermoplasty were followed for 5 years [37•]. Respiratory adverse events were fewer after treatment as compared to 12 months pretreatment, and this reduction persisted through 5 years in the 12 subjects that were followed for the full duration of the extension study. Hospitalizations per year decreased by 70 % as compared to the pretreatment rate, and there was a three-fold reduction in the rate of emergency department visits per year (pre-treatment 0.36/patient/year, posttreatment 0.12/patient/year). Medication usage and lung function did not meaningfully change in years 2–5 posttreatment.

In the AIR2 extension study, 162 out of 190 subjects that received bronchial thermoplasty were available 5 years post-treatment [38•]. The proportion of subjects who experienced a

severe exacerbation remained around 30 % for each year of the 5-year follow-up period, as compared to 51.6 % in the 12 months before thermoplasty. Compared to the pretreatment period, there was an 88 % reduction in emergency department visits at year 5, nearly identical to that seen in year 1. Though lung function did not improve, nearly 30 % of subjects were able to decrease ICS dosage by 50 % or more. High-resolution computed tomography (HRCT) images did not change in most of the 93 subjects that were evaluated before and after thermoplasty, and only one subject was noted to have new bronchiectasis posttreatment, though it is unclear whether this was related to bronchial thermoplasty or to the progression of severe asthma [39]. Importantly, subjects who did not achieve an improvement in AQLQ of at least 0.5 had higher rates of severe exacerbations, emergency department visits, and hospitalizations than those who did achieve an improvement in AQLQ of at least 0.5. Schatz et al. noted that impaired asthma-specific quality of life was associated with more emergency department visits [40]. Taking these findings together, this suggests that improving AQLQ predicts future exacerbation rates and is a good way to separate those who derive benefit from bronchial thermoplasty (“responders”) and those who did not (“non-responders”). In summary, these studies show that bronchial thermoplasty appears to have acceptable long-term safety with benefits that persist to at least 5 years, although the number of subjects treated is not large enough to rule out rare adverse events.

Where Should Bronchial Thermoplasty Fit in Asthma Therapy?

Recently, the Global Initiative for Asthma (GINA) guidelines recommended that bronchial thermoplasty be considered as

step 5 therapy in some adult patients with severe asthma that remains uncontrolled despite use of recommended therapeutic regimens (level of evidence, B) [41]. Despite proven benefit and safety, access to bronchial thermoplasty is limited by high initial cost and lack of coverage by insurance providers. Although a cost-effective analysis of bronchial thermoplasty is not available, it seems likely that the upfront cost of approximately US\$25,000 or more for bronchial thermoplasty is offset by the large reduction in health care utilization in patients with high rates of severe exacerbations, whose direct and indirect medical care costs can exceed \$12,000 annually [6].

Further work is needed to identify which patients with severe asthma respond to bronchial thermoplasty. HRCT is useful as a non-invasive assessment of airway wall thickening and remodeling [42] as well as gas trapping [43] and can provide a global assessment of pathologic changes in the asthmatic lung. The use of HRCT in addition to spirometry, questionnaires, and other routinely measured variables can allow for the phenotyping of patients with severe asthma to better potentially identify a priori who may respond to bronchial thermoplasty, thereby allowing for judicious allocation of limited resources to those who would derive the greatest benefit. In our experience, patients with small airway disease (as defined by increased HRCT gas trapping) are less likely to achieve an improvement in AQLQ scores as compared to those with large airway disease, suggesting that HRCT measures of asthma pathology can predict response to bronchial thermoplasty [44]. The identification of patients who are most likely to respond to bronchial thermoplasty is an important unanswered question.

In our clinical practice, patients who arrive on high-dose ICS and LABA combinations are initially evaluated for

Selecting Bronchial Thermoplasty

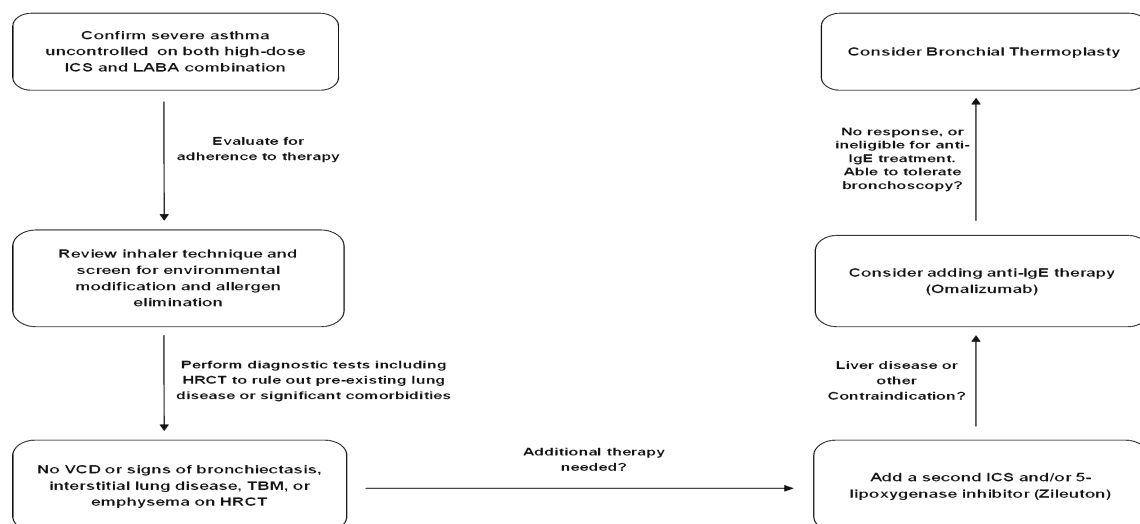


Fig. 3 Suggested algorithm for when to perform bronchial thermoplasty

adherence to therapy, which can be alarmingly low [45]. We review inhaler technique with each patient and perform an extensive screen for environmental modification and allergen elimination. In addition, we screen patients for other contributing diseases (such as vocal cord dysfunction (VCD), rhinosinusitis, and GERD) and treat them as indicated. In addition, we also schedule a high-resolution computed tomography (HRCT) chest to ensure no preexisting bronchiectasis, interstitial lung disease, tracheobronchomalacia (TBM), or emphysema that would suggest a potential non-asthma source of respiratory symptoms as well to evaluate the airways prior to bronchial thermoplasty treatment. In severe asthma patients who need additional therapy, we often start with a second inhaled corticosteroid and/or consider adding a 5-lipoxygenase inhibitor (zileuton) if there is no active liver disease or other contraindications. In patients who do not achieve adequate control of asthma symptoms with the above interventions, we consider anti-IgE therapy with omalizumab in those with documented sensitivity to aeroallergens. Patients who do not achieve an adequate response to or are otherwise ineligible for omalizumab are evaluated for bronchial thermoplasty (Fig. 3). If no contraindication is found, these patients undergo bronchial thermoplasty by an experienced bronchoscopist at our site. It is unclear whether bronchial thermoplasty should be reserved as a last option or be implemented earlier in the treatment of severe asthma. Further work which is necessary to identify precisely when asthma providers should consider bronchial thermoplasty as treatment is escalated, as it is possible that performing bronchial thermoplasty earlier in the course of asthma could be cost effective in reducing long-term health care utilization.

Conclusions

In summary, bronchial thermoplasty is an effective and safe therapy for severe asthma that can improve asthma-specific quality of life and reduce severe exacerbations. Unlike biologic therapy, bronchial thermoplasty does not require long-term treatment, thereby placing the entire cost of therapy up front. The identification of patients who respond best to bronchial thermoplasty will be an important step in increasing the availability of this novel procedure to those who would benefit the most.

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Compliance with Ethics Guidelines

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