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Review Article

BRONCHIAL THERMOPLASTY IN THE MANAGEMENT OF SEVERE BRONCHIAL ASTHMA IN ADULTS: A REVIEW

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ABSTRACT

Severe bronchial Asthma also known as severe refractory asthma is defined as asthma requiring treatment with high dose corticosteroids(ICS) and long-acting bronchodilators (LABA) or leukotriene modifier/ theophylline plus a second controller (and/or systemic steroids) that is uncontrolled despite the treatment as per guidelines of The European Respiratory Society (ERS)/American Thoracic Society (ATS) for severe asthma. Bronchial Thermoplasty (BT) is an advanced device-based medical therapy, used as a treatment option for patients 18 years and older whose bronchial asthma is not well controlled with inhaled corticosteroids and long-acting beta-agonists. Bronchial thermoplasty provides therapeutic benefit by delivering radiofrequency thermal energy to the airway wall during bronchoscopy to reduce airway remodeling and bronchoconstriction. This treatment therapy further provides long-term improvement in the quality of life-related to asthma and reduction in severe asthma exacerbation and health care utilization in patients with severe persistent asthma who are unresponsive to maximum clinical therapy. The use of bronchial thermoplasty for the treatment of severe asthma was approved by the Food and drug administration (FDA). The approval was primarily based on a randomized controlled trial known as Asthma Intervention Research (AIR) 2 published in 2010. This review summarizes the published clinical trials and observational studies showing the role of bronchial thermoplasty as a new and emerging FDA approved nonpharmacological treatment option for patients with severe bronchial asthma.

Keywords: Severe Bronchial Asthma, Airway remodeling, Alair Bronchial thermoplasty, AIR trial

INTRODUCTION

Asthma is the most prevalent global health problem affecting more than 358 million people worldwide. [1] It is a chronic inflammatory disease of the airways characterized as bronchial hyperreactivity, bronchial constriction, excessive mucous secretion and varying degrees of airway obstruction. Chronic airway inflammation causes an increase in the airway smooth muscle (ASM) thickness further causing bronchial constriction and breathing difficulties leading to irreversible structural changes of the airways in bronchial asthma, termed as airway remodeling, signified as major pathological features of severe asthma.[2]The American Thoracic Society/European Respiratory Society guidelines consider asthma to be severe if the patient requires treatment with high-dose ICS and LABA or leukotriene modifier/theophylline and/or systemic steroids for most of the past year to prevent asthma from becoming uncontrolled, or if it remains uncontrolled despite this therapy. Uncontrolled asthma might manifest as poor symptom control, frequent or severe exacerbations, and airflow limitation on bronchodilator withdrawal. The management of severe bronchial asthma represents the foremost difficult aspect of asthma and has been addressed in the ERS/ATS guidelines on severe asthma. Patients with severe bronchial asthma have reduced life-expectancy and experience substantial morbidity due to poorly controlled asthma and the adverse effects of high-dose corticosteroids. [3-5] The financial burden of severe asthma is high due to frequent hospital visits, medication, and irregular work schedules. Severe asthma persists in most patients, particularly in those with low socioeconomic status and greater co morbidities. Several standard maintenance medications are being used in a stepwise approach for treatment and good prognosis but still challenging for poorly controlled asthma. Bronchial thermoplasty is one of the emerging device-based therapy for patients with severe asthma nonresponsive to maximal pharmacological therapies like high dose Inhaled corticosteroid(ICS) and long-acting bronchodilators(LABA). [6] Studies have shown that patients with severe asthma have extensive airway remodeling because of increased airway smooth muscle and airway hyperresponsiveness leading to bronchial constriction which may not a response to anti-inflammatory therapies and other medications.[7, 8]

Description of the Procedure:

Bronchial thermoplasty is a bronchoscopy based advanced treatment option for patients with severe asthma by delivering local radiofrequency (RF) energy to all visible large airways performed with Alair bronchial thermoplasty system. [9] BT system consists of the Alair Radiofrequency (RF) Controller and the Alair catheter with an expandable four-electrode basket at one end and a deployment handle at another end. The catheter is introduced through a 2-mm working channel of a standard 5-mm fiberoptic bronchoscope. Once the catheter is in the specified area the 4-electrode array at the catheter tip is expanded for airway walls contact and is activated to deliver RF electrical energy at a controlled temperature of 65° Cover 10 seconds. A thermocouple attached to one arm of the electrode array monitors the temperature at the tissue surface and other parameters to provide continuous feedback to the RF Controller for controlling the distribution of energy. [10] Patients are treated with 50 mg of steroid three days pre-procedure, on the day of the procedure, and after the procedure. Nebulized albuterol (2.5-5 mg) is given before the patient undergoes screening spirometry to

assess forced expiratory volume in 1 second (FEV1) and repeated before the procedure. BT is performed via fiberoptic bronchoscopy either through an oral or nasal approach under moderate to deep sedation or general anesthesia and in three bronchoscopic sessions with an interval of approximately 3 weeks, as mentioned in previous studies. [9, 11] The procedure usually takes 30 to 60 minutes and generally well tolerated. The treatment should be performed systematically in a nonoverlapping manner in all visible airways beginning from the right lower lobe, left lower lobe and gradually bilateral upper lobes in 3 sessions. The right middle lobe is not treated, as it may lead to complications like transient obstruction of right middle lobe, further atelectasis, and right middle lobe syndrome. Each of the lower lobes is delivered with around 40 RF activations and 60 RF activations to the combined upper lobes to achieve an improvement in the ACQ score of 0.5. The lung segments previously treated with RF energy should be monitored carefully not to have retreated as it might cause complications like hemorrhage and bronchiectasis. After each procedure, there should be a careful assessment of gag reflex, vital signs, and forced expiratory volume in 1 second (FEV1≥80% of pre-BT FEV1 that day)). Respiratory complications may arise within the first week and worsen symptoms gradually resolving within another week. Recurrent lung atelectasis secondary to fibrin plugs, lung abscess, and pneumothorax has been reported to occur as an early complication of bronchial thermoplasty. [12-14] So patients should be advised for increased use of bronchodilators, mucous clearance techniques, and systemic corticosteroids after the procedure.

Criteria for Patient Selection:

The major inclusive criteria for bronchial thermoplasty are patients diagnosed should be between 18 and 65 years old and diagnosed with moderate-to-severe persistent asthma according to the guidelines of the Global Initiative for Asthma.[6].Prebronchodilator should be FEV1 ≥ 60% and there should have been a history of uncontrolled asthma despite treatment with high dose inhaled corticosteroids and long-acting beta-agonists with additional leukotriene modifiers and/or anti-IgE.; nonsmoker for a minimum of 1 year with ACQ score >1.5 and AQLQ score ≤6.25.[15]Patients undergoing bronchial thermoplasty should provide written informed consent. The main exclusion criteria include the history of life-threatening severe asthma, known sensitivity to medications necessary for bronchoscopy, Respiratory diseases like emphysema, cystic fibrosis, upper airway obstruction, atelectasis, history of more than 4 admissions for lower respiratory tract infections, uncontrolled hypertension, implanted electrical device and other medical conditions interfering with the procedure.

Mechanism of Action:

Studies have shown that patients with severe bronchial asthma have extensive airway remodeling due to increased airway smooth muscle and airway hyperresponsiveness leading to bronchial constriction which may not a response to anti-inflammatory drug therapies and other medications.[7, 8]Bronchial thermoplasty aims at reducing the thickness of airway smooth muscle in patients with these patients by generating radiofrequency thermal energy through a catheter that causes ASM atrophy without damaging the superficial mucosa.[16] This treatment improves a patient's respiration by reducing the airways' ability to constrict airflow. Severe asthma patients who underwent bronchial thermoplasty during clinical trials have

demonstrated significant clinical improvement in their symptoms and also a reduction in severe asthma exacerbations and hospital emergency room visits for respiratory-related complications. This has been demonstrated in preclinical studies and confirmed histologically in human airways. The first study of Bronchial thermoplasty was performed preoperatively in a patient with lung cancer which had no complications and resulted in a significant reduction of smooth muscle mass in the airways on followup.[11] The ASMATHERM, A Bicentric Prospective Study, evaluating Bronchial thermoplasty in Patients Presenting Severe Uncontrolled Asthma) was performed in 15 patients with severe asthma by Pretolani and colleagues [17] showed that the reduction in airway smooth muscle mass correlated with the improvement in asthma flareup control and quality of life and decrease in severe exacerbation at first year after bronchial thermoplasty. In a study of 26 patients with severe persistent asthma, clinical improvements were seen in airway wall thickness and gas trapping in MDCT one year after bronchial thermoplasty.[18].In small observational studies of patients with severe asthma post-bronchial thermoplasty found improvements in measurements of small airway dysfunction assessed with oscillometry [19]Bronchial thermoplasty has shown to decrease airway smooth muscle and type 1 collagen deposition underneath basement membrane.[17, 20, 21]

Human trials in Bronchial thermoplasty:

Several randomized controlled trials were evaluated to see the clinical benefits of bronchial thermoplasty in the treatment of severe bronchial asthma. The first nonrandomized prospective study was done was published in 2006 by Cox et al including 16 patients with mild to moderate asthma (forced expiratory volume per second, FEV1, > 80%). [9] The primary objective of the study was to evaluate the safety of BT, airway hyperresponsiveness, and lung function during 2 years which showed no deterioration in respiratory health status. An improvement in prebronchodilator FEV1 (% predicted) was observed at 12 weeks and 1 year, however, no significant changes were observed in prebronchodilator and postbronchodilator FEV1 (%predicted) at 2-year follow-up and chest computed tomogram (CT). These patients had normal lung function but showed airway hyperresponsiveness (mean methacholine PC20: 0.92 mg/mL at baseline, 4.75 mg/mL at 12 weeks, 5.45 mg/mL at 1 year, and 3.40 mg/mL at 2 years post procedure), and most subjects were not on high-dose ICS or ICS/LABA combination. Also, there was a rise in peak expiratory flow rates and an increase in symptom-free days (47% versus 73%) which was measured at 12 weeks post-procedure. This analysis showed that BT was well tolerated by patients with bronchial asthma and that there were no serious adverse effects related to the procedure. Limitations of this study included the lack of a control group and a small number of subjects.

The first multicenter, randomized study named Asthma Intervention Research(AIR), conducted by Thomson et al. in 112 patients with moderate to severe asthma which compared BT with Inhaled corticosteroids (ICS)and long-acting B2-agonists (LABA) or ICS/LABA therapy alone. [15] The major objective of this study was to evaluate the frequency of mild exacerbations at 3, 6, and 12 months (at a 2-week withdrawal period from LABA). The results indicated that the BT group experienced approximately 10 fewer mild exacerbations per subject per year in comparison to the control group. The BT group showed a greater number

of symptom-free days, lesser need for rescue medication, and lung function improvement like morning peak expiratory flow (PEF), airway hyper-responsiveness(PC20) in quality of life measured by AQLQ (Asthma Quality of Life Questionnaire), and in (ACQ) Asthma Control Questionnaire scores. There have been no significant differences between the BT and control group in FEV1, nor AHR.

In addition to AIR trial another major randomized study, RISA trial (Research in Severe Asthma), [22] was done in 2007 by Thomson et al.in 32 patients (15 in the BT group, 17 patients in the control group) according to Global Initiative for Asthma (GINA) criteria for severe persistent asthma and one patient under American Thoracic Society (ATS) criteria for refractory asthma. [4] The primary objective of this study was to assess the safety and efficacy of BT in patients with severe asthma. Post BT, the study was divided into several phases of reduced steroid use and weaning. Bronchial thermoplasty showed significant short term risks and frequent rate of hospitalization in early phases of treatment but gradually in 52 weeks significant long term improvement was detected in FEV1 (% predicted), controlled asthma, lesser use of rescue medication, reduction in use of ICS and withdrawal of oral corticosteroids in steroid weaning phase compared to the control group. The study additionally indicated that Bronchial thermoplasty can be safely performed in populations with severe refractory asthma. In the reduced steroid phase, the BT subjects showed significantly greater improvement from baseline in short-acting bronchodilators use, AQLQ, and ACQ compared with the control subjects. However, this study was unblinded, unlike the AIR study that indicates the possibility of a placebo effect further influencing the possible outcomes. [22]

The third RCT conducted AIR 2 trial, (Asthma Intervention Research 2) is the largest multicenter, randomized, double-blind, sham-controlled, clinical trial conducted in 288 adult patients with severe asthma refractory to high dose ICS and long-acting β2-agonists. [23]. The study evaluated the safety and efficacy of BT, and changes in quality of life compared to a baseline assessed by the AQLQ at 6, 9 and 12 months post-procedure. All the patients underwent three bronchoscopies performed three weeks apart conducted by an unblinded bronchoscopy team and followup was done by the unblinded assessment team. The primary outcome of interest was an increase in the AQLQ score from baseline. AOLQ score of ≥0.5 was significantly greater among those treated with BT than with patients who underwent sham bronchoscopy (79% vs 64%). The Bronchial thermoplasty group, in comparison to the sham control group, additionally indicated a decreased frequency of severe asthma exacerbations (by 32%), a decreased incidence of hospitalization (by 73%), a decreased number of medical visits (by 84%), and a reduced number of days absent from work/school (by 66%). There was a 36% risk reduction in the subjects of the BT group than in the Sham group (27.3 vs. 42.9%) reporting worsening of asthma. The adverse effects were resolved by standard therapy, except hemoptysis, which occurred in one patient after BT and required embolization of the bronchial artery. It appears that the benefits of BT over the sham group show long term improvement in severe, uncontrolled bronchial asthma outweigh the short-term, increased risk of adverse effects. There are already results from a five-year follow-up of patients after treatment with BT. The method has proven to be safe, and no deterioration in lung function (FEV1, FVC – Forced Vital Capacity) was observed. Furthermore, there were no severe complications such as

pneumothorax, mechanical ventilation, cardiac arrhythmias, or death resulting from the procedure. Also, high resolution computed tomography (HRCT) pairs from the AIR 2 group were evaluated at year 5, and there were no findings of new, abnormal structural changes in the airways, such as bronchial stricture, bronchiolitis obliterans, or new pulmonary emphysema (compared to previous HRCT), that could have resulted from the procedure. These results validate the findings of two previous randomized, controlled studies that compared BT with usual care without a sham control. [22, 23]

A prospective, multicenter, open-label, single-arm study named PAS2 (Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma) study was started in 2017 which compared the clinical outcomes of patients treated with bronchial thermoplasty with the AIR2 study. PAS2 study was designed to evaluate the short- and long-term efficacy and safety of bronchial thermoplasty. 284 patients registered in this study from 2011 to 2014 at 27 centers in the USA and Canada out of which 279 patients were treated with bronchial thermoplasty. [24] In the beginning, the study enrolled the first 190 PAS2 subjects when a compared 165 patients completed a 3-year follow-up visit, which could be made. The PAS2 study showed clinical improvements in the severe asthma patients similar to the outcomes in the AIR2 trial.[23, 25].The hospitalization rate of severe bronchial asthma exacerbation after 3 years was reduced by 44.6%% and 39.99% in comparison to the 12 months before treatment which was better than the results of the AIR 2 study by 36.8% and 25% respectively.[23].The patients enrolled in the PAS2 study were comparatively severe than in the AIR2 trial (94.7% vs 82.1%), had a longer duration of asthma history(25.6 vs 22.9 years), had more age(45.9 vs 40.7) and BMI (32.5 vs 29.3) respectively. Also, the subjects of the PAS2 study had a significant reduction in medication use from 18.9% at baseline to 10.2% after 3years post bronchial thermoplasty [24] There was an increased incidence of chronic sinus disease in the participants. There was no significant change in pulmonary function test after bronchial thermoplasty. However, there was a significant improvement in post-bronchodilator FEV1 following treatment with bronchial thermoplasty.from 84.8% at baseline to 82.3% at the 3year follow-up visit similar to the results of the AIR2 trial. The procedure-related respiratory complications in the PAS2 study were similar to the AIR2 trial. The PAS2 study suggests the safety of bronchial thermoplasty use in severe asthmatic patients further decreasing hospitalization rates, emergency room visits, and asthma flare-ups compared to 12 months before the treatment validating the results of AIR2 trial. [23, 24] This study indicates the effectiveness and safety of bronchial thermoplasty in the improvement of quality of life in patients with poorly controlled asthma. Limitations of this study include the selection of a particular geographical location, unlike the AIR2 trial that was done globally. Also, the data collected in this study is of patients completing 3 years follow-up though the study is ongoing for 5 years period.So further analysis and studies will be more valuable for further confirming the effectivity of the bronchial thermoplasty procedure.

Financial Considerations:

Currently, the role of the effective use of bronchial thermoplasty is uncertain. The impact of adding bronchial thermoplasty (BT) for a specified patient group was compared with severe, poorly controlled asthma treated with standard drug regimen with or without adjuvant omalizumab (OMAL) in Italy ,which showed the

high cost of BT initially, but gradually reduction in emergency room visits and hospitalizations and increase in economic savings by the fifth year.[26] Also in USA study was conducted using the Markov model comparing the cost-effectiveness of bronchial 10 year period. The outcome showed that bronchial thermoplasty has shown to be cost-effective in the treatment of high-risk patients with severe uncontrolled and poorly controlled bronchial asthma. [27] Another Markov model-based analysis was conducted assessing 5-year healthcare utilization, patient quality of life and adverse events. in commercially insured patients, which showed BT as a cost-effective option for poor controlled severe asthma. [28]

CONCLUSION

Bronchial thermoplasty is an innovative device-based therapy delivered by the Alair system for patients with severe asthma. Different randomized controlled trials have shown to have significant improvements in clinical outcomes and asthma-related quality of life in people. So clinicians should consider these types of new therapeutic procedures for the management of severe bronchial asthma. Bronchial thermoplasty is the only treatment therapy targeting airway smooth muscle further resulting in diminished bronchial constriction and asthma exacerbation. Long term follows up of patients in different studies has also demonstrated a long term reduction in hospital visits and frequent asthma exacerbations. So currently bronchial thermoplasty is considered as a beneficial nonpharmacological treatment option in adult patients with severe and poorly controlled bronchial asthma.

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