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Bronchial Thermoplasty in the Treatment of Severe Asthma

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ABSTRACT

Asthma is a chronic inflammatory airway disease with several distinct phenotypes, characterized by different immunopathological pathways, clinical presentation, severity of the disease, and response to treatment. The phenotypes of asthma include eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic asthma. Approximately 3.6-10% of patients with asthma have severe refractory disease, which is unresponsive to high dose inhaled corticosteroids (ICS), and long-acting β2-agonists (LABA). Most patients with eosinophilic asthma are responsive to corticosteroids, and interleukin-targeted biologics, whereas, patients from other phenotypes, such as neutrophillic and paucigranullocytic asthma are resistant to treatment with ICS and biotherapeutics. The hallmark of severe refractory asthma is airway hyperresponsiveness, and remodeling. Histopathologically, patients with severe asthma have airway smooth muscle (ASM) hyperplasia and hypertrophy; subepithelial basement membrane thickening and fibrosis; all which contribute to fixed airflow limitation. Severe refractory asthma is very difficult to treat pharmacologically. It requires innovative therapies, such as bronchial thermoplasty which reduces the hypertrophied ASM mass and relieves the AHR, and bronconconstriction. Bronchial thermoplasty has been shown to improve asthma control, reduce severe exacerbations, hospitalizations, emergency room visits, and improve the quality of life, which persist up to 5 years following the procedure.

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Introduction

Asthma is a significant public health problem, affecting more than 358 million individuals globally,and its prevalence has been increasing during the last 40 years. It is the most common chronic respiratory disease in children in the developed countries, and the prevalence of asthma is steadily increasing in the developing world [1-5]. Asthma is a chronic inflammatory airway disease with several distinct phenotypes, characterized by different immunopathological pathways, clinical presentation, severity of the disease, and response to treatment [6-11]. Induced sputum cytometry is the gold standard biomarker for the diagnosis of the four phenotypes of asthma, such as eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic asthma [7].

Patients with eosinophilic asthma have an eosinophil count of ≥3%, whereas patients with neutrophilic asthma have elevated sputum neutrophil count between ≥61%, and ≥64% [12-15]. Mixed granulocytic phenotype is characterized by an increase in both eosinophils (>3%), and neutrophils (>61% or >64%). Paucigranuocytic phenotype embraces patients with very few eosinophils (<3%), and neutrophils (<61% or <64%) in induced sputum [14-16]. Non-eosinophilic asthma is the term used to classify patients with low eosinophil numbers (<3%), which include neutrophilic asthma, and paucigranulocytic phenotype [7].

Most patients with eosinophilic asthma are responsive to with high dose inhaled corticosteroids, and to anti-interleukin antagonists (ALI) targeted against eosinophilic asthma. Conversely, other phenotypes of asthma, such as neutrophilic and paucigranulocytic asthma are unresponsive to treatment with ICS, LABA, LTRA, and biologics. The currently approved biologics for the treatment of Th2-driven eosinophilic asthma include omalizumab (anti-IgE); and interleukin monoclonal antibodies, such as mepolizumab, and reslizumab (anti-IL-5), benralizumab (anti-IL-5R), dupilumab (anti-IL-4α/13), and tezepelumab (anti-TSLP). However, there are no marketed biotherapeutics for the treatment of neutrophilic and paucigranulocytic asthma.

Severe refractory asthma is characterized by airway hyperresponsiveness (AHR) and remodeling. Histopatho pathologically, patients with severe asthma have airway smooth muscle (ASM) hyperplasia and hypertrophy; subepithelial basement membrane thickening and fibrosis; all which contribute to fixed airflow limitation. Severe refractory asthma is very difficult to treat pharmacologically. It requires innovative therapies, such as bronchial thermoplasty which reduces the hypertrophied ASM mass and relieves the AHR, and bronchoconstriction.

Severe Refractory Asthma

Approximately 3.6-10% of patients with asthma have severe refractory disease, with persistent symptoms, frequent exacerbations, hospitalizations, and frequent emergency room visits. This subgroup of patients has fixed airflow limitation (low FEV1), and is difficult to control despite treatment with high dose inhaled corticosteroids (ICS), long-acting β2-agonists LABA), and leukotriene receptor antagonists (LTRA) [17-19]. Therefore,this subgroup of patients require more targeted therapies, especially patients with high medication requirements and persistent symptoms and exacerbations. Severe refractory asthma consists of different phenotypes that have poorly controlled asthma, and has been referred to as refractory asthma, steroid-dependent and/or

resistant asthma, difficult-to-control, and brittle asthma [20,21]. This subgroup of patients is now termed as severe refractory asthma, and includes patients who remain poorly controlled despite an extensive re-evaluation and an observation period of at least 6 months by an asthma specialist [22]. The definition, evaluation and treatment of severe refractory asthma has been refined, and continues to be updated [22-24]. The ATS guidelines on the definition of severe refractory asthma is based on two major and seven minor criteria for the diagnosis of severe refractory asthma.20 The criteria for established diagnosis of refractory asthma include fulfilling one, or both major criteria and at least two minor criteria [20]. The ATS criteria for the diagnosis of severe refractory asthma are given in Table 1.

Table 1: American Thoracic Society Criteria for severe/refractory asthma

Major criteria
Treatment with continuous or near continuous (>50% of the year) oral corticosteroids
Need for treatment with high-dose inhaled corticosteroids
Minor criteria
Need for additional daily treatment with controller medication (long-acting β2-agonist, leukotriene receptor antagonist, theophylline)
Asthma symptoms needing short-acting β2-agonists use on a daily or near daily basis
Persistent airway obstruction (FEV1 <80% predicted, diurnal peak flow variability <20% predicted
One or more urgent care visit for asthma
Three or more oral steroid bursts per year
Prompt deterioration with >25% reduction in oral or inhaled corticosteroids
Near fatal asthma event in the past
Diagnosis: One major criterion plus two minor criteria; other diseases should have been excluded, exacerbating factors treated, and patient is general adherent

Airway Remodeling

The pathophysiological feature of severe refractory asthma is airway hyperresponsiveness, and airway remodeling, which contribute to persistent fixed airway obstruction, and poor lung function (low FEV1). There is a strong correlation between airway remodeling and progression of airflow limitation in patients with severe asthma[25].Airway remodeling and bronchoconstriction in severe asthma involves structural changes, such as airway smooth muscle hyperplasia and hypertrophy; subepithelial basement membrane (SBM) thickening and fibrosis; extracellular matrix (ECM) protein deposition; hypertrophy of the submucous glands, goblet cell hyperplasia, thickening and shedding of the epithelium, and neovascularization [26-33].

Airway smooth muscle hypertrophy, hyperplasia, and changes in phenotype of ASM is considered the main factor involved in airway hyperresponsiveness. Patients with severe refractory asthma have airway smooth muscle cell hyperplasia and hypertrophy, especially patients with fixed airflow limitation [33-36]. ASM hypertrophy and hyperplasia is associated with progressive decline in lung function, persistent asthma, and unresponsiveness corticosteroids [36-40]. Table 2 summarizes the pathophysiological feaures of severe refractory asthma.

Table 2: Pathophysiological features of airway remodeling in patients with severe refractory asthma

Epithelial injury due to allergens, respiratory viral infections, and pollutants
Release of cytokines, chemokines, growth factors, and adhesion molecules
Airway epithelial thickening, shedding, and further release of "alarmin" cytokines
Submucous glands and goblet cell hyperplasia, and mucus hypersecretion
Airway hyperresponsiveness
Subepithelial basement membrane fibrosis, and thickening
Deposition of extracellular matrix proteins
Mast cell infiltration of airway smooth muscle cells
Activation of myofibroblasts, and fibroblasts
Airway smooth muscle hyperplasia, and hypertrophy
Neoangiogenesis, and exaggerated vasodilatation Airway remodeling

Airway smooth muscle cells are active secretory cells, which display plasticity depending on the inflammatory milieu. They display pro-inflammatory and immunomodulatory functions by synthesis and expression of a variety of surface molecules, integrins, and Toll-like receptors [41, 42]. Activation of a variety of receptors on ASM cells can lead to production and secretion of several pro-inflammatory mediators, which may act in an autocrine or paracrine fashion [30]. ASM cells have been reported to secrete several pro-inflammatory cytokines (IL-1β, IL-8, IL-5, IL-6, IL-8, IL-10, and IL-11); chemokines (eotaxins, and Gro-α); growth factors (EGF-1, FGF, PDGF; VEGF, and IGF-1); and angiogenic factors (VEGF, angiogenin, and angiopoietin) [31-41, 42]. In addition, ASM cells from asthmatic patients have a distinct hyperreactive "primed" phenotype, which is characterized by increased release of pro-inflammatory cytokines, chemokines, and growth factors [29-42]. Table 3 shows the list of airway smooth muscle cell secretory products, and surface receptors.

Table 3: Standard drugs used for the treatment of asthma

Inhaled β2-agonist
Short acting (salbutamol, levalbuterol, terbutaline, pirbuterol)
Long-acting (salmeterol, formeterol)
New long-acting (indacaterol, olodaterol, vilanterol)
Combination of LABA and inhaled corticosteroids
Salmetrol and fluticasone (Advair Diskus)
Formeterol and budesonide (Symbicort)
Vilanterol and fluticasone
Triple combo (Vilanterol, fluticosone and umeclidium)
Cromones
Cromlyn sodium, nedocromil sodium
Inhaled anti-cholinergics
Short-acting (ipratropium bromide)
Long-acting (oxitropium bromide, tiotropium bromide)
New long-acting (umeclidium bromide, glycopyrrolate)
Corticosteroids
Betamethasone dipropionate
Budenoside, fluticasone, flunisolone
Ciclesonide, mometasone
Oral methylxanthines
Rapid release theophyllines
Sustained release theophyllines (Theo-24, Theocron, Uniphyl)
Phosphodiesterase (PDE)-4 inhibitor (roflumilast)
Leukotriene receptor antagonists
Montelukast, pranlukast
Cinalukast, zafirlukast
5-lipoxygenase inhibitors
Zileuton

Airway remodeling in asthma is accompanied by deposition of extracellular matrix protein in the reticular basement region, lamina propria, and submucosa, which contributes to airway wall thickening, and airflow obstruction. In addition, there is an increase in the numbers of airway resident cells, such as fibroblasts, myofibroblasts, and ASM cells [36, 41-43]. These cells are capable of producing pro-inflammatory mediators, which orchestrate and amplify the inflammatory responses. The ECM proteins consists of higher amount of collagen I, III, V, fibronectin, tenascin, lumicans, glycosaminoglycans, proteoglycans, and elastic fibers [40,41]. The composition of the proteins in patients with severe asthma is different from that in non-asthmatic subjects [44]. Extracellular matrix proteins, and mediators released by mast cells, T lymphocytes, and ASM cells may modulate ASM phenotype, and functions, including proliferation, migration and contraction [45, 46].

Histopathologically, severe refractory asthma is characterized by thickening and fibrosis of the subepithelial reticular basement membrane (SRBM) in both adults and children with asthma [43, 47-51]. Payne et al. have demonstrated that SRBM thickening is already present in children with difficult to treat asthma, and to a similar extent to that seen in adults with severe asthma. In addition they found that the reticular basement membrane thickening is not associated with age, symptom duration, lung function, or concurrent eosinophilic airway inflammation.Thus, reticular membrane thickening and fibrosis can occur in different phenotypes of severe refractory asthma, and even in children with difficult to treat asthma. Furthermore, thickening and fibrosis of the SRBM is associated with airway responsiveness to methacholine [51, 52].

Thickening of the subepithelial reticular basement membrane is due to increased deposition of collagen I and III, tenascin, fibronectin, versican, laminin, and lumican, produced mainly by fibroblasts, and to a lesser extent myofibroblasts [47-50]. The increase in subepithelial basement membrane thickness has been shown to correlate with ASM hypertrophy, and parallels the severity of airflow limitation [53]. Thickening of the reticular memebrane and fibrosis may contribute to corticosteroid unresponsiveness [54].The airway epithelium provide a physical and immunological protective barrier against inhaled micro-organisms, allergens, and pollutants. Patients with severe refractory asthma exhibit epithelial thickening, shedding, apoptosis of ciliated epithelial cells, and exposure of sensitive neuronal terminals [55-57]. Inflamed airway epithelium, particularly due to viral respiratory infections secrete 'alarmin' cytokines (Il-25, IL-33, TSLP), and is associated with upregulation of growth factors [58, 59]. The extent of epithelial injury correlates with increasing AHR and the severity of asthma [52, 60]. Interleukin-25, IL-33, and growth factors (e.g., TGF-β) are fibrotic cytokines, and may promote ASM cell proliferation, subepithelial fibrosis, and airway remodeling.

Treatment of Severe Refractory Asthma
Severe refractory asthma has classically been treated using stepwise guidelines of increasing drugs and dosages depending on the severity of the disease, such as the Global Initiative for Asthma (GINA) guidelines, and the National Asthma Education and Prevention Program (NAEPP) [23]. The GINA strategy recommends intensification of the treatment according to the severity of asthma, based on the treatment required to control, and reduce symptoms and exacerbations. The classic GINA guidelines have five levels of treatments, which steps-up treatment according to severity. Steps 1 to 3 are classified as mild-moderate asthma, and steps 4 and 5 are classified as moderate-severe disease. The current paradigm recommends use of low dose ICS and LABA (formoterol), and SABA as required at step 1. The GINA step-wise

guidelines recommend treatment with low dose ICS, and LABA at step 2, followed by increasing the dosage of ICS up to 800 μg/day, and LABA to achieve control at step 3. In patients with severe asthma, steps 4 and 5, the dosage of ICS is increased up to 2000 μg/day, and therapeutic alternatives, such as leukotriene receptor antagonists (LTRA), slow-release theophyllines, or long-acting muscarinic antagonist (LAMA) are added to the regimen [1]. Table 3 classifies the standard drugs used to treat asthma.

The GINA guideline, and NAEPP yardsticks for step-up treatment recommend initiation of biologics, such as anti-IgE, and anti-interleukin (IL)-5 monoclonal antibodies for patients with eosinophilic asthma at step 5. The guidelines also suggest a trial of chronic macrolide therapy to reduce asthma exacerbations in persistent symptomatic or uncontrolled patients at step 5.The latest ERS/ATS Task Force guidelines recommend using anti-IL-5 and anti-IL-5 receptor α for severe uncontrolled adult eosinophilic asthma phenotypes, using a blood eosinophil cut-point of 150 μL-1 to guide anti-IL-5 initiation in adult patients with severe asthma. The guidelines suggest using tiotropium for adolescents and adults with severe asthma uncontrolled asthma despite GINA step 4-5, or NAEPP step 5 therapies [1, 23]. The Task Force also suggests a trial of macrolide therapy to reduce exacerbation in persistently symptomatic,or uncontrolled patients on GINA step 5 or NAEPP step 5 therapies, irrespective of asthma phenotype. Additionally, the ERS/ATS guidelines suggest using ant-IL-4/13 (dupilumab) for adult patients with severe eosinophilic asthma, and for those with severe corticosteroid-dependent asthma regardless of blood eosinophil counts.

Despite treatment according to guidelines, monitoring adherence, and adequate inhaler technique, a significant proportion of asthma patients do not achieve adequate control with the standard treatment, including high dose ICS, LABA, LTRA, and interleukin antagonists [1]. Between 49% and 53% of adults receiving treatment adequately have poorly controlled asthma [61, 62], and up to 64% of adolescent patients have asthma that is inadequately controlled by the currently available therapies [63].

There are several phenotypes of asthma associated with different co-morbidities, and response to treatment. Patients with severe refractory asthma require phenotyping with sputum cell cytometry, serum biomarkers, bronchoscopy, or transthoracic CT scans, as an initial step in the management of asthma, in order to give the right patient the right treatment [(6-8),(14,64-66),(21,67),(68-70)].The hallmark of severe refractory asthma is exuberant ASM hyperplasia and hypertrophy, deposition of ECM proteins, and subepithelial reticular membrane fibrosis; and progressive airway remodeling. Bronchial thermoplasty is a non-pharmacological therapy targeting airway wall thickening, due to ASM hypertrophy, and subepithelial fibrosis, which are responsible for AHR, persistent fixed airflow limitation, and recurrent bronchospasms.

Bronchial Thermoplasty
The mainstay pharmacotherapy for severe asthma is high dose ICS, LABA, LTRA, and addition of biologics for patients with eosinophilic asthma at step 5 of the GINA and NAEPP guidelines [1, 23]. However, corticosteroids and biologics do not suppress ASM cell hyperplasia and hypertrophy, and subepithelial fibrosis which are the histopathological features of severe refractory asthma responsible for airflow limitation, and excessive bronchoconstriction [71].Brochial thermoplasty (BT) is a strategic therapy aimed at reducing the hypertrophied ASM mass in patients with severe refractory asthma [72,73]. BT is a bronchoscopic treatment recommended for subjects aged

18 and above with severe persistent asthma not responding to high dose ICS, LABA, and eosinophilic interleukin antagonists. BT is suggested for all the phenotypes of asthma characterized by ASM hypertrophy, and uncontrolled asthma on the standard therapies, including biologics, and corticosteroid dependent or resistant patients.

Bronchial thermoplasty is a complex procedure and should be performed in highly specialized centers. The selection and preparation of patients for BT is rigorous, and the the procedure should be performed by experienced pulmonologists or bronchoscopists [73-76]. Patients for bronchial thermoplasty should be in an optimal stable condition, without any asthma exacerbation or respiratory infection for at least 2 weeks prior to the procedure. In addition to their standard medical treatment for severe asthma, they should be pre-treated with prednisone 50 mg/day for 3 days before BT, on the day of BT, and the day after bronchial thermoplasty. Patients with low FEV1 <80% should have the procedure postponed until their spirometry results improve. Before the procedure, all patients should be pre-treated with nebulized salbutamol and/or ipratropium bromide [76].

Bronchial thermoplasty is performed under moderate-to-deep sedation or general anesthesia [73-76]. At bronchoscopy a special disposable AlairTM catheter with a distal diameter of 1.4 mm, and a basket-like array of expandable electrodes is inserted through the instrument channel. Optimal thermoplasty of all subsegment bronchi is successful with ultrathin, rotatable bronchoscopes with increased ease of use and higher degree of flexibility [76]. The AlairTM catheter delivers controlled electromagnetic energy generated by a radiofrequency (RF) generator (AlairTM Bronchial Thermoplasty System, Natick, MA, USA) [77, 78]. The AlairTM catheter electrode delivers targeted radiofrequency energy to the bronchial airway wall, and results in reduction of the hypertrophied airway smooth muscle mass, which is the major cause of severe bronchoconstriction [75-83]. The procedure also decreases subepithelial fibrosis, extracellular matrix, submucous glands, airway nerve endings, epithelial cells, and neuroendocrine cells [73, 75, 76, 82].Bronchial thermoplast may reduce neuroendocrine cells, bronchial nerve terminals, and destroy TRPV1 nerve receptors, and the unmyelinated C-fibers in the submucosa, and interrupt central and local axonal reflexes responsible for bronchoconstriction, and airway hyprresponsiveness [84,85]. Bronchial thermoplasty is given over three bronchoscopy sessions at approximately 20 days intervals, one for each lower lobe and one for both upper lobes [75, 76, 79]. Radiofrequency electrical energy delivered by a radiofrequency (RF) generator is applied to the airways distal to the mainstem bronchi between 3 and 10 mm in diameter throughout the tracheobronchial tree, except for the right middle lobe [76, 79, 80, 83]. In practice, 40-70 RF activations are delivered in the lower lobes, and between 50 and 100 activations in the upper lobes combined depending on the patient's size and airway caliber [76]. Traditionally, the right middle lobe (RML) is typically avoided due to concerns about the right middle lobe syndrome [86]. The right middle lobe bronchi has a narrow orifice and is more likely to be obstructed by post-procedure inflammation leading to atelectasis and the RML syndrome [76]. In experienced centers, RML thermoplasty has been performed without the complication of the RML syndrome [87].

The AlairTM Bronchial Thermoplasty System (Boston Scientific, Natick, MA, USA) uses continuous feedback to tightly control the degree of tissue heating to avoid bronchial perforation, scorching, bleeding, and stenosis [76,77]. The AlairTM catheter delivers radiofrequency energy to warm the airway wall to a

targeted temperature of 65°C, which reduces the ASM mass by approximately 50% after 3-6 weeks after the procedure [76, 79, 83].

Bronchial thermoplast is a complex procedure and should be performed in centers with adequate preparation and experience to handle possible intra- and post-procedural complications [88]. It requires proper preparation and management of patients pre- and post-thermoplasty. Additionally, It requires identification of the right patients, implementation of proper BT technique, and intense post-procedural care and long-term follow-up [73].The procedure should be performed meticulously to avoid bronchospasms, airway edema, and bleeding. Minor radiological features occur following BT, and a chest X-ray should be performed after the procedure. Bronchial thermoplasty is a safe and efficacy procedure, however, it is associated with a short-term increase in asthma-related symptoms, such as cough and sputum production, exacerbations, and hospital admissions for asthma during the post-thermoplasty phase, which usually resolves within few weeks [73, 76, 89]. Computed tomography scans show specific radiological patterns in the airways directly exposed to RF energy, and some distal airways and lung parenchyma not directly treated by BT. These radiological changes usually resolve in most patients within 1-6 months [89,90]. Occasionally, bronchiectasis, atelectasis, and rarely pneumothorax and lung cysts, have been observed as complications following the bronchial thermoplasty. One case report describes hemoptysis associated with necrosis of a bronchial nodule which resolved by the third session of bronchial thermoplasty [91-94]. Table 4 summerizes the complications of bronchial thermoplasty.

Table 4: Complications of bronchial thermoplasty

Worsening of asthma control
Hospital re-admissions
Severe exacerbations
Cough with sputum production
Hemoptysis
Acute mild CT peribronchial infiltration
Nasopharyngitis
Pulmonary infection
Lung abscess
Central bronchiectasis
Upper lobe atelectasis
Collapse of airway by mucous plugging
Pulmonary cysts and pneumothorax

Several randomized controlled trials, and prospective multicenter studies in Australia, Canada, France, Japan, Netherland, Spain, UK, and USA in patients with severe uncontrolled asthma have documented improvement in asthma symptoms, fewer severe exacerbations, and hospitalization, and emergency room visits, which persist up to 5 years following bronchial thermoplasty [75, 76, 78, 89-97]. Bronchial thermoplasty has also been reported to improve the quality of life, and daily living by allowing patients to participate in their normal duties and activities.

The first randomized unblinded clinical trial (Asthma Intervention Research [AIR] 1) in 112 patients with moderate-to-severe asthma was investigated by Cox and colleagues [98]. Patients treated with BT showed a significant reduction in mild exacerbations compared with pre-bronchial thermoplasty. On the other hand, there were no changes in the frequency of exacerbations in the control group. There were significant improvements in asthma control assessed by the Asthma Control Questionnaire (ACQ), and quality of life assessed by the Asthma Quality of Life Questionnaire(AQLQ) scores in the BT-treated patients compared with controls 98]. However, there were no differences in FEV1 or airway hyperresponsiveness (defined as a provocative concentration of methacholine required to lower the FEV1 by 20% (PC20) or less than 8 mg/mL [98].

The second randomized unblinded clinical trial was the Research in Severe Asthma (RISA) trial.This trial which studied 32 patients with severe asthma for the safety and efficacy of BT, reported a significant improvement in the asthma control, quality of life, rescue medication use, and pre-bronchodilator FEV1 in BT-treated subjects compared with control subjects. The beneficial effects of bronchial thermoplasty persisted even after reduction in the dosages of ICS and OCS, suggesting that BT may have a steroid-sparing effect [99].The largest randomized double-blind sham-controlled trial was the Asthma Intervention Research 2 (AIR2) trial in 297 patients with severe asthma which compared BT with a sham procedure [100]. The AIR2 trial reported significant improvement in AQLQ scores, reduction in the frequency of severe exacerbations, and decrease in emergency department visits, and days lost from work or school in the year after bronchial thermoplasty compared with treatment with sham procedure [100].

Chupp, et al [101].compared the outcome of BT after a follow-up of 3 years in 190 Post-FDA Approved Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma (PAS2) subjects with 190 bronchial thermoplasty-treated subjects in the AIR2 trial at 3 years of follow-up. At year 3 after BT, the percentage of PAS2 subjects with severe exacerbations, emergency department visits, and hospitalizations significantly decreased by 45%, 55%, and 40% respectively, resembling the AIR2 results [100,101]. The PAS2 study showed similar improvements in asthma control after BT compared with the AIR2 trial despite enrolling subjects who had poorer asthma control [101]. After 3-year follow-up, PAS2 subjects were able to significantly reduce their mean ICS dose to 2070 µg/day, whereas, the AIR2 subjects significantly reduced their mean ICS to 1841 µg/day[101]. Previous observational studies on the effectiveness of bronchial thermoplasty for severe asthma have reported reductions in exacerbations, and/or a step-down in treatment in 50-75% of patients undergoing the procedure [94-96,97].

A systemic review of the long-term safety of BT in the AIR, RISA, and AIR2 trials demonstrated no long-term decline in FEV1, no change in the number of emergency room visits or hospitalization for adverse respiratory events [102]. The reduction in exacerbations seen in the first year after remained stable for up to 5 years [73,102-105]. Radiologically, follow-up CT scans performed on the subgroup of the treated patients demonstrated no evidence of bronchiectasis and bronchial stenosis [106]. Recently, Chaudhuri, et al [106]. have reported that after 10 years post-thermoplasty the AQLQ scores, and frequency of severe exacerbation were comparable to those recorded 1 year after bronchial thermoplasty. This suggests that the beneficial effects of bronchial thermoplasty may be sustained for up to 10 years or longer.

Bronchial thermoplasty has a long-term safety profile, and may be considered for patients with predominant chronic airflow obstruction, and patients who do not respond to anti-IgE, anti-interleukin biologics, and macrolides [73,107,108]. Patients with neutrophilic, and paucigranulocytic asthma are suitable candidates for bronchial thermoplasty because they have excessive ASM hypertrophy, hyperplasia and hyperresponsiveness. They are unresponsive to treatment with high-dose ICS, LABA, LTRA, and interleukin antagonists targeted against eosinophilic asthma. Another group of patients who may benefit from BT are patients resistant to corticosteroid, or on high dose oral/injection steroids, in order to minimize adverse effects from the steroids [109].The indications, patients selection, and contraindication for bronchial thermoplasty are very well stipulated by Thomson, and Bonta and colleagues[75,76].

The US Food and Drug Administration (FDA) approved BT in 2010 as a safe procedure indicated for the treatment of severe persist asthma in patients 18 years and older, that is not controlled with high-dose ICS, and LABA[77]. BT is also approved in several EU countries, Australia, Canada, Japan, Korea, UK, and USA. The British guidelines on the management of asthma states that bronchial thermoplasty can be considered for the treatment of adult patients (aged 18 and over) with severe asthma who have poorly controlled asthma despite optimal therapy [110]. The The GINA guidelines recommend bronchial thermoplasty for the treatment of severe corticosteroid-resistant asthma at step 5[1]. We also recommend BT at GINA step 5 in patients with Th2-low asthma, including neutrophilic and paucigranulocytic asthma who are uncontrolled on high dose ICS, eosinophilic interleukin antagonists, and macrolide antibiotics [111].

Conclusion
Severe refractory asthma is characterized by persistent symptoms, with frequent severe exacerbations, and hospitalizations. It consumes a large proportion of the pharmo-economical resources in most healthcare systems. Severe asthma is associated with fixed airflow obstruction, and low FEV1. The hallmark of severe refractory asthma is ASM hyperplasia and hypertrophy, increase in ECM proteins, and subepithelial basement membrane fibrosis, which all lead to fixed airflow limitation. Severe refractory asthma is unresponsive to high dose ICS, LABA, and LTRA, and to interleukin antagonist targeted against eosinophilic asthma. It requires specific therapeutic interventions aimed at preventing, and reducing airway remodeling, such as bronchial thermoplasty. BT has been shown to be safe and effective in improving symptoms, reducing severe exacerbation, improving the quality of life, and allowing patient to carry on their daily living.

Conflicts of interest
The author reports no conflicts of interest in this manuscript.

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